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| (54) Title: 4-SUBSTITUTED-4-PIPERIDINE CARBOXAMIDE DERIVATIVES (57) Abstract 4-substituted-4-piperidine carboxamides of Formula (I) are antagonists of VLA-4 and/or $\alpha 4\beta 7$, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders. | | |

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TITLE OF THE INVENTION

4-SUBSTITUTED-4-PIPERIDINE CARBOXAMIDE DERIVATIVES

BACKGROUND OF THE INVENTION

5 The present invention relates to novel 4-substituted-4-piperidinecarboxamide derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

10 Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules
15 (CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without interfering with normal cellular functions is essential for an effective and safe
20 therapeutic agent that inhibits cell-cell and cell-matrix interactions.

 The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of α and β heterodimeric, transmembrane receptor molecules found in various combinations on nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell,
25 67, 1033 (1991); T. A. Springer, Cell, 76, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. 14, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, Ed.; Acad. Press, NY, 1996, p. 191).

30 VLA-4 ("very late antigen-4"; CD49d/CD29; or $\alpha 4\beta 1$) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, and is a key mediator of the cell-cell and cell-matrix interactions of leukocytes (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes."

Ann. Rev. Immunol. **8**, 365 (1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells at sites of inflammation and on dendritic and macrophage-like cells. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in Cellular and Molecular Mechanisms of Inflammation, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", Immunol. Today, **14**, 506 (1993). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-Verlag, NY, 1990.) A role for VLA-4/CS-1 interactions in inflammatory conditions has been proposed (see M. J. Elices, "The integrin $\alpha_4\beta_1$ (VLA-4) as a therapeutic target" in Cell Adhesion and Human Disease, Ciba Found. Symp., John Wiley & Sons, NY, 1995, p. 79).

$\alpha_4\beta_7$ (also referred to as LPAM-1 and $\alpha_4\beta_p$) is an integrin expressed on leukocytes and is a key mediator of leukocyte trafficking and homing in the gastrointestinal tract (see C. M. Parker et al., Proc. Natl. Acad. Sci. USA, **89**, 1924 (1992)). The ligands for $\alpha_4\beta_7$ include mucosal addressing cell adhesion molecule-1 (MadCAM-1) and, upon activation of $\alpha_4\beta_7$, VCAM-1 and fibronectin (Fn). MadCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells of gut-associated mucosal tissues of the small and large intestine ("Peyer's Patches") and lactating mammary glands. (See M. J. Briskin et al., Nature, **363**, 461 (1993); A. Hamann et al., J. Immunol., **152**, 3282 (1994)). MadCAM-1 can be induced *in vitro* by proinflammatory stimuli (See E. E. Sikorski et al. J. Immunol., **151**, 5239 (1993)). MadCAM-1 is selectively expressed at sites of lymphocyte extravasation and specifically binds to the integrin, $\alpha_4\beta_7$.

Neutralizing anti- α_4 antibodies or blocking peptides that inhibit the interaction between VLA-4 and/or $\alpha_4\beta_7$ and their ligands have proven efficacious both prophylactically and therapeutically in

several animal models of disease, including i) experimental allergic encephalomyelitis, a model of neuronal demyelination resembling multiple sclerosis (for example, see T. Yednock et al., "Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha_4\beta_1$ integrin." Nature, 356, 63 (1993) and E. Keszthelyi et al., "Evidence for a prolonged role of α_4 integrin throughout active experimental allergic encephalomyelitis." Neurology, 47, 1053 (1996)); ii) bronchial hyperresponsiveness in sheep and guinea pigs as models for the various phases of asthma (for example, see W. M. Abraham et al., " α_4 -Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. 93, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte recruitment and bronchial hyperresponsiveness in the guinea-pig." Eur. J. Pharmacol., 282, 243 (1995)); iii) adjuvant-induced arthritis in rats as a model of inflammatory arthritis (see C. Barbadillo et al., "Anti-VLA-4 mAb prevents adjuvant arthritis in Lewis rats." Arthr. Rheuma. (Suppl.), 36 95 (1993) and D. Seiffge, "Protective effects of monoclonal antibody to VLA-4 on leukocyte adhesion and course of disease in adjuvant arthritis in rats." J. Rheumatol., 23, 12 (1996)); iv) adoptive autoimmune diabetes in the NOD mouse (see J. L. Baron et al., "The pathogenesis of adoptive murine autoimmune diabetes requires an interaction between α_4 -integrins and vascular cell adhesion molecule-1." J. Clin. Invest., 93, 1700 (1994), A. Jakubowski et al., "Vascular cell adhesion molecule-Ig fusion protein selectively targets activated α_4 -integrin receptors in vivo: Inhibition of autoimmune diabetes in an adoptive transfer model in nonobese diabetic mice." J. Immunol., 155, 938 (1995), and X. D. Yang et al., "Involvement of beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MadCAM-1) in the development of diabetes in nonobese diabetic mice", Diabetes, 46, 1542 (1997)); v) cardiac allograft survival in mice as a model of organ transplantation (see M. Isobe et al., "Effect of anti-VCAM-1 and anti-VLA-4 monoclonal antibodies on cardiac allograft survival and response to soluble antigens in mice." Transplant. Proc., 26, 867 (1994) and S. Molossi et al., "Blockade of very late antigen-4 integrin binding to

fibronectin with connecting segment-1 peptide reduces accelerated coronary arteriopathy in rabbit cardiac allografts." J. Clin. Invest., **95**, 2601 (1995)); vi) spontaneous chronic colitis in cotton-top tamarins which resembles human ulcerative colitis, a form of inflammatory bowel disease (see D. K. Podolsky et al., "Attenuation of colitis in the Cotton-top tamarin by anti- α_4 integrin monoclonal antibody.", J. Clin. Invest., **92**, 372 (1993)); vii) contact hypersensitivity models as a model for skin allergic reactions (see T. A. Ferguson and T. S. Kupper, "Antigen-independent processes in antigen-specific immunity.", J. Immunol., **150**, 1172 (1993) and P. L. Chisholm et al., "Monoclonal antibodies to the integrin α_4 subunit inhibit the murine contact hypersensitivity response." Eur. J. Immunol., **23**, 682 (1993)); viii) acute neurotoxic nephritis (see M. S. Mulligan et al., "Requirements for leukocyte adhesion molecules in nephrotoxic nephritis.", J. Clin. Invest., **91**, 577 (1993)); ix) tumor metastasis (for examples, see M. Edward, "Integrins and other adhesion molecules involved in melanocytic tumor progression.", Curr. Opin. Oncol., **7**, 185 (1995)); x) experimental autoimmune thyroiditis (see R. W. McMurray et al., "The role of α_4 integrin and intercellular adhesion molecule-1 (ICAM-1) in murine experimental autoimmune thyroiditis." Autoimmunity, **23**, 9 (1996); and xi) ischemic tissue damage following arterial occlusion in rats (see F. Squadrito et al., "Leukocyte integrin very late antigen-4/vascular cell adhesion molecule-1 adhesion pathway in splanchnic artery occlusion shock." Eur. J. Pharmacol., **318**, 153 (1996)). The primary mechanism of action of such antibodies appears to be the inhibition of lymphocyte and monocyte interactions with CAMs associated with components of the extracellular matrix, thereby limiting leukocyte migration to extravascular sites of injury or inflammation and/or limiting the priming and/or activation of leukocytes.

There is additional evidence supporting a possible role for VLA-4 interactions in other diseases, including rheumatoid arthritis; various melanomas, carcinomas, and sarcomas; inflammatory lung disorders; atherosclerotic plaque formation; restenosis; and circulatory shock (for examples, see A. A. Postigo et al., "The $\alpha_4\beta_1$ /VCAM-1

adhesion pathway in physiology and disease.”, Res. Immunol., 144, 723 (1994) and J.-X. Gao and A. C. Issekutz, “Expression of VCAM-1 and VLA-4 dependent T-lymphocyte adhesion to dermal fibroblasts stimulated with proinflammatory cytokines.” Immunol. 89, 375 (1996)).

5 At present, there is a humanized monoclonal antibody (Antegren® Athena Neurosciences/Elan) against VLA-4 in clinical development for the treatment of “flares” associated with multiple sclerosis and a humanized monoclonal antibody (ACT-1® LeukoSite) against $\alpha 4\beta 7$ in clinical development for the treatment of inflammatory
10 bowel disease. Several peptidyl antagonists of VLA-4 have been described (D. Y. Jackson et al., “Potent $\alpha 4\beta 1$ peptide antagonists as potential anti-inflammatory agents”, J. Med. Chem., 40, 3359 (1997); H. N. Shroff et al., “Small peptide inhibitors of $\alpha 4\beta 7$ mediated MadCAM-1 adhesion to lymphocytes”, Bioorg. Med. Chem. Lett., 6, 2495 (1996); US
15 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973). There is one report of nonpeptidyl inhibitors of the ligands for $\alpha 4$ -integrins (WO96/31206).
There still remains a need for low molecular weight, specific inhibitors of VLA-4- and $\alpha 4\beta 7$ -dependent cell adhesion that have improved
20 pharmacokinetic and pharmacodynamic properties such as oral bioavailability and significant duration of action. Such compounds would prove to be useful for the treatment, prevention or suppression of various pathologies mediated by VLA-4 and $\alpha 4\beta 7$ binding and cell adhesion and activation.

25

SUMMARY OF THE INVENTION

 The compounds of the present invention are antagonists of the VLA-4 integrin (“very late antigen-4”; CD49d/CD29; or $\alpha 4\beta 1$) and/or the $\alpha 4\beta 7$ integrin (LPAM-1 and $\alpha 4\beta p$), thereby blocking the binding of
30 VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or $\alpha 4\beta 7$ to its various ligands, such as MadCAM-1, VCAM-1 and fibronectin. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment,

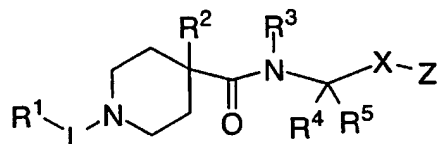
- prevention and suppression of diseases mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, such as multiple sclerosis, asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ
- 5 transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds of Formula I

15



I

or a pharmaceutically acceptable salt thereof wherein:

- | | | |
|------|------|----------------------------------------------|
| L is | 1) | -C(O)-, |
| 20 | 2) | -O-C(O)-, |
| | 3) | -NR ^e -C(O)-, |
| | 4) | -S(O) ₂ -, |
| | 5) | -P(O)(OR ⁴)-, |
| | 6) | -C(O)C(O)-; |
| 25 | X is | 1) a bond or |
| | | 2) C(R ⁶)(R ⁷); |
| | Z is | 1) -C(O)OR ^d , |
| | | 2) -P(O)(OR ^d)(OR ^e) |
| | | 3) -P(O)(R ^d)(OR ^e) |
| 30 | | 4) -S(O) _m OR ^d , |
| | | 5) -C(O)NR ^d R ^h , or |
| | | 6) -5-tetrazolyl; |

- R¹ is
- 1) C₁-10alkyl,
 - 2) C₂-10alkenyl,
 - 3) C₂-10alkynyl,
 - 4) Cy,
 - 5) Cy-C₁-10alkyl,
 - 6) Cy-C₂-10alkenyl,
 - 7) Cy-C₂-10alkynyl,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R² is 1) a group selected from R¹;
- R³ is
- 1) hydrogen,
 - 2) C₁-10alkyl optionally substituted with one to four substituents independently selected from R^a, or
 - 3) Cy optionally substituted with one to four substituents independently selected from R^b,

- R⁴ is
- 1) hydrogen,
 - 2) C₁-10alkyl,
 - 3) C₂-10alkenyl,
 - 4) C₂-10alkynyl,
 - 5) Cy, or
 - 6) Cy-C₁-10alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R⁵ is
- 1) hydrogen,
 - 2) C₁-10alkyl,
 - 3) C₂-10alkenyl,
 - 4) C₂-10alkynyl,
 - 5) Cy-(Cy¹)_p,
 - 6) Cy-(Cy¹)_p-C₁-10alkyl,
 - 7) Cy-(Cy¹)_p-C₂-10alkenyl,
 - 8) Cy-(Cy¹)_p-C₂-10alkynyl,

alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a ; and Cy and Cy^1 are optionally substituted with one to four substituents independently selected from R^b ;

- 5 R^6 is
- 1) hydrogen,
 - 2) a group selected from R^a , or
 - 3) a group selected from R^1 ;
- R^7 is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 10 3) C₂₋₁₀alkenyl,
 - 4) C₂₋₁₀alkynyl,
 - 5) Cy, or
 - 6) Cy C₁₋₁₀alkyl,

wherein alkyl, alkenyl, alkynyl are optionally substituted with one to
 15 four substituents selected from R^a , and Cy is optionally substituted with one to four substituents independently selected from R^b ;

- R^a is
- 1) -CF₃;
 - 2) -OR^d,
 - 3) -NO₂,
 - 20 4) halogen
 - 5) -S(O)_mR^d,
 - 6) -CR^d(N-OR^e),
 - 7) -S(O)₂OR^d,
 - 8) -S(O)_mNR^dRe,
 - 25 9) -NR^dRe,
 - 10) -O(CR^fR^g)_nNR^dRe,
 - 11) -C(O)R^d,
 - 12) -CO₂R^d,
 - 13) -CO₂(CR^fR^g)_nCONR^dRe,
 - 30 14) -OC(O)R^d,
 - 15) -CN,
 - 16) -C(O)NR^dRe,
 - 17) -NR^dC(O)Re,
 - 18) -OC(O)NR^dRe,

- 19) $-NR^dC(O)OR^e$, or
 20) $-NR^dC(O)NR^dR^e$;
 R^b is
 1) a group selected from R^a ,
 2) C_{1-10} alkyl,
 5 3) C_{2-10} alkenyl,
 4) C_{2-10} alkynyl,
 5) Cy, or
 6) Cy- C_{1-10} alkyl,
 wherein alkyl, alkenyl, alkynyl, and Cy are optionally substituted with a
 10 group independently selected from R^c ;
 R^c is
 1) halogen,
 2) amino,
 3) carboxy,
 4) C_{1-4} alkyl,
 15 5) C_{1-4} alkoxy,
 6) hydroxy,
 7) aryl,
 8) aryl C_{1-4} alkyl, or
 9) aryloxy;
 20 R^d and R^e are independently selected from the group consisting of
 1) hydrogen,
 2) C_{1-10} alkyl,
 3) C_{2-10} alkenyl,
 4) C_{2-10} alkynyl,
 25 5) Cy, and
 6) Cy C_{1-10} alkyl,
 wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one
 to four substituents independently selected from R^c ; or
 R^d and R^e together with the atoms to which they are attached form a
 30 heterocyclic ring of 5 to 7 members containing 0-2 additional
 heteroatoms independently selected from oxygen, sulfur and nitrogen;
 R^f and R^g are independently selected from hydrogen, C_{1-10} alkyl, Cy and
 Cy C_{1-10} alkyl; or

R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

- R^h is
- 1) hydrogen,
 - 2) C_{1-10} alkyl,
 - 3) C_{2-10} alkenyl,
 - 4) C_{2-10} alkynyl,
 - 5) cyano,
 - 6) aryl,
 - 7) aryl C_{1-10} alkyl,
 - 8) heteroaryl,
 - 9) heteroaryl C_{1-10} alkyl, or
 - 10) $-SO_2R^i$;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a ; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b ;

- R^i
- 1) C_{1-10} alkyl,
 - 2) C_{2-10} alkenyl,
 - 3) C_{2-10} alkynyl, or
 - 4) aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c ;

Cy and Cy^1 are independently selected

- 25
- 1) cycloalkyl,
 - 2) heterocyclyl,
 - 3) aryl, and
 - 4) heteroaryl;

m is 0, 1 or 2;

- 30 n is an integer from 1 to 10; and
 p is 0 or 1.

A subset of compounds of formula I are compounds wherein R^1 is C_{1-10} alkyl, Cy or $Cy-C_{1-10}$ alkyl wherein alkyl and Cy are optionally substituted as provided above. For the purpose of R^1 Cy is

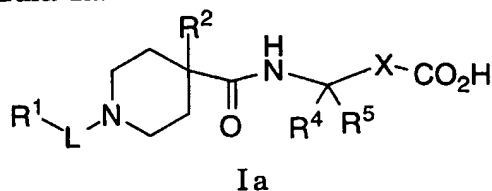
preferably aryl optionally substituted with one or two substituents independently selected from R^b.

Another subset of compounds of formula I are compounds wherein L is SO₂ or C(O). Preferably L is SO₂.

- 5 Another subset of compounds of formula I are compounds wherein R² is C₁-10alkyl, Cy-C₁-10alkyl or Cy each optionally substituted as provided above. For the purpose of R² Cy is preferably aryl.

In another subset of formula I Z is C(O)OR^d.

- 10 A preferred embodiment of compounds of formula I are compounds of formula Ia:



wherein

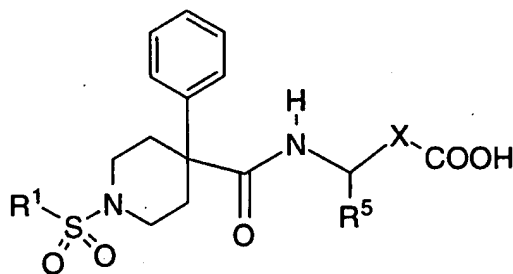
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|----|-------------------|----|--------------------------------------|
| 15 | L is | 1) | -C(O)- or |
| | | 2) | -S(O) ₂ ; |
| | X is | 1) | a bond or |
| | | 2) | C(R ⁶)(R ⁷); |
| | R ¹ is | 1) | C ₁ -10alkyl, |
| 20 | | 2) | Cy, or |
| | | 3) | Cy-C ₁ -10alkyl, |

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

- | | | | |
|----|-------------------|----|----------------------------------------|
| 25 | R ² is | 1) | a group selected from R ¹ ; |
| | R ⁴ is | 1) | hydrogen; |
| | R ⁶ is | 1) | hydrogen, or |
| | | 2) | a group selected from R ¹ ; |
| | R ⁷ is | 1) | hydrogen; |

- 30 all the other variables are as defined above under formula I.

Another preferred embodiment of compounds of formula I are compounds of formula Ib:



Ib

- X is
- 1) a bond or
 - 2) CH₂;
- 5 R¹ is
- 1) C₁-10alkyl,
 - 2) Cy, or
 - 3) Cy-C₁-10alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy is optionally substituted with

- 10 one to two substituents independently selected from R^b;

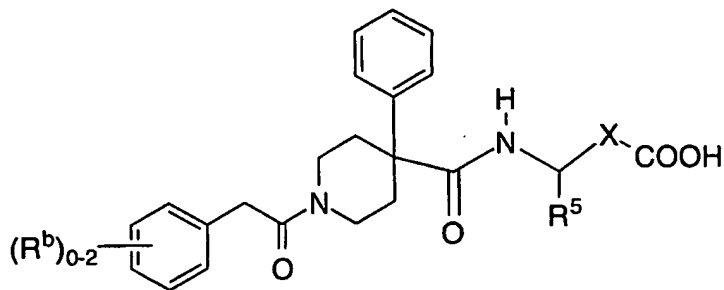
- R⁵ is
- 1) hydrogen,
 - 2) C₁-10alkyl,
 - 3) Cy-(Cy¹)_p, or
 - 4) Cy-(Cy¹)_p-C₁-10alkyl,

- 15 wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy and Cy¹ are optionally substituted with one to two substituents independently selected from R^b; Cy and Cy¹ are independently

- 1) aryl; and

- 20 all other variables are as defined under formula I.

Another preferred embodiment of compounds of formula I are compounds of formula Ic:



Ic

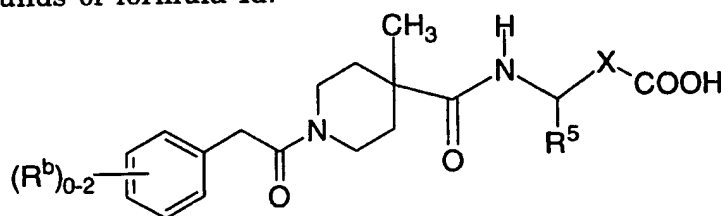
- X is
- 1) a bond or
 - 2) CH₂;
- R⁵ is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 3) Cy-(Cy¹)_p, or
 - 4) Cy-(Cy¹)_p-C₁₋₁₀alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy and Cy¹ are optionally substituted with one to two substituents independently selected from R^b; Cy and Cy¹ are independently

- 1) aryl; and

all other variables are as defined under formula I.

Another preferred embodiment of compounds of formula I are compounds of formula Id:



Id

- X is
- 1) a bond or
 - 2) CH₂;
- R⁵ is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 3) (Cy¹)_p, or
 - 4) (Cy¹)_p-C₁₋₁₀alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy and Cy¹ are optionally substituted with one to two substituents independently selected from R^b; Cy and Cy¹ are independently

- 1) aryl; and

all other variables are as defined under formula I.

Representative compounds of the present invention have been provided in the Examples section hereinbelow.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or
5 branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or
10 combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or
15 combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 10 carbon atoms. The term also includes monocyclic ring fused to an aryl group in which the point of
20 attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. The term also includes aryl group fused to a
25 monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like.

"Heteroaryl" means a mono- or bicyclic aromatic ring
30 containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl,

benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

- "Heterocyclyl" means mono- or bicyclic saturated rings containing at least one heteroatom selected from N, S and O, each of said
- 5 ring having from 3 to 10 atoms. The term also includes monocyclic heterocycle fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolyl,
- 10 tetrahydroisoquinolyl, dihydroindolyl, and the like.

"Halogen" includes fluorine, chlorine, bromine and iodine.

The following abbreviations are used:

| | |
|-------------|-------------------------------------------------------------------------|
| BOC (boc) | t-butyloxycarbonyl |
| calc. | calculated |
| CBZ (Cbz) | benzyloxycarbonyl |
| DCC | dicyclohexylcarbodiimide |
| DIEA | diisopropylethylamine |
| DMAP | 4-(N,N-dimethylamino)pyridine |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| EDC | 1-(3-dimethylaminopropyl)3-ethylcarbodiimide |
| | HCl |
| EtOAc | ethyl acetate |
| FAB-MS | fast atom bombardment-mass spectroscopy |
| Fmoc (Fmoc) | fluorenylmethoxycarbonyl |
| HBTU | 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| HOBt | 1-hydroxybenzotriazole hydrate |
| HPLC | high pressure liquid chromatography |
| Me | methyl |
| MHz | megahertz |
| NBS | N-bromosuccinimide |
| NMP | N-methylpyrrolidin-2-one |
| NMR | nuclear magnetic resonance |

| | |
|-------|---------------------------|
| Ph | phenyl |
| Pr | propyl |
| prep. | prepared |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single
5 enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both
10 E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol
15 tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl
20 acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using
25 optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids

including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly
5 preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine,
10 betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-dibenzylethylenediamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine,
15 piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids,
20 including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-
25 toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically
30 acceptable salts.

Utilities

The ability of the compounds of Formula I to antagonize the actions of VLA-4 and/or $\alpha 4\beta 7$ integrin makes them useful for preventing

or reversing the symptoms, disorders or diseases induced by the binding of VLA-4 and or $\alpha 4\beta 7$ to their various respective ligands. Thus, these antagonists will inhibit cell adhesion processes including cell activation, migration, proliferation and differentiation. Accordingly, another aspect of the present invention provides a method for the treatment (including prevention, alleviation, amelioration or suppression) of diseases or disorders or symptoms mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, which comprises administering to a mammal an effective amount of a compound of Formula I. Such diseases, disorders, conditions or symptoms are for example (1) multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) allergic conjunctivitis, (5) inflammatory lung diseases, (6) rheumatoid arthritis, (7) septic arthritis, (8) type I diabetes, (9) organ transplantation rejection, (10) restenosis, (11) autologous bone marrow transplantation, (12) inflammatory sequelae of viral infections, (13) myocarditis, (14) inflammatory bowel disease including ulcerative colitis and Crohn's disease, (15) certain types of toxic and immune-based nephritis, (16) contact dermal hypersensitivity, (17) psoriasis, (18) tumor metastasis, (19) hepatitis, and (20) atherosclerosis.

20

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

30

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound

of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

- 5 In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more
10 preferably from about 10 mg to about 100 mg) of a compound of Formula I per kg of body weight per day.

- For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of Formula I in an acceptable
15 ophthalmic formulation may be used.

Pharmaceutical Compositions

- Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula
20 I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from
25 combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a
30 compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical,

parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention
5 comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to
10 salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal
15 inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the
20 present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for
25 inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions,
30 dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms

depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, 5 alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid 10 preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may 15 be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

20 Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water 25 emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the 30 active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable

machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound
 5 moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

10

| <u>Injectable Suspension (I.M.)</u> | <u>mg/mL</u> |
|-----------------------------------------------|--------------|
| Compound of Formula I | 10 |
| Methylcellulose | 5.0 |
| Tween 80 | 0.5 |
| 15 Benzyl alcohol | 9.0 |
| Benzalkonium chloride | 1.0 |
| Water for injection to a total volume of 1 mL | |

20

| <u>Tablet</u> | <u>mg/tablet</u> |
|----------------------------|------------------|
| Compound of Formula I | 25 |
| Microcrystalline Cellulose | 415 |
| Povidone | 14.0 |
| Pregelatinized Starch | 43.5 |
| Magnesium Stearate | <u>2.5</u> |
| 25 | 500 |

30

| <u>Capsule</u> | <u>mg/capsule</u> |
|-----------------------|-------------------|
| Compound of Formula I | 25 |
| Lactose Powder | 573.5 |
| Magnesium Stearate | <u>1.5</u> |
| | 600 |

AerosolPer canister

Compound of Formula I 24 mg

| | |
|---------------------------------|---------|
| Lecithin, NF Liquid Concentrate | 1.2 mg |
| Trichlorofluoromethane, NF | 4.025 g |
| Dichlorodifluoromethane, NF | 12.15 g |

5 Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) other VLA-4 antagonists such as those described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973, WO96/31206 and WO98/42656; (b) steroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) immunosuppressants such as cyclosporin, tacrolimus, rapamycin and other FK-506 type immunosuppressants; (d) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripeleminamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (e) non-steroidal anti-asthmatics such as β 2-agonists (terbutaline, metaproterenol,

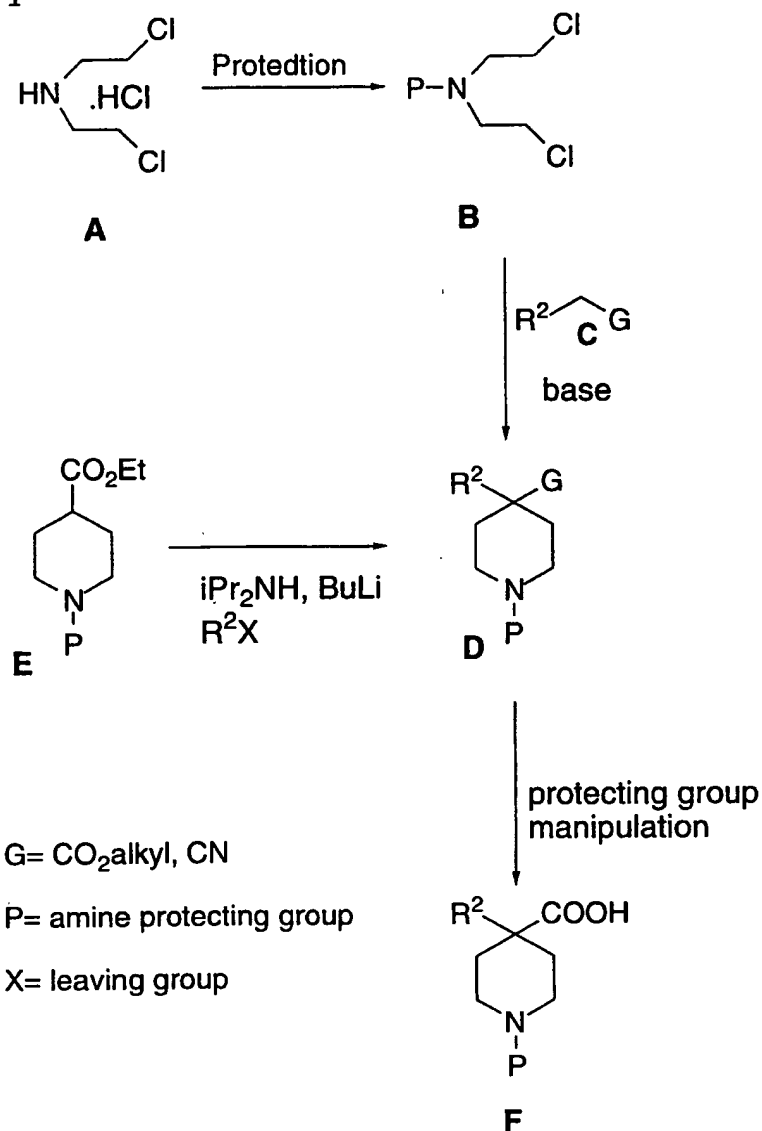
- fenoterol, isoetharine, albuterol, bitolterol, salmeterol and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (zafirlukast, montelukast, pranlukast, iralukast, pobilukast, SKB-106,203), leukotriene biosynthesis inhibitors
- 5 (zileuton, BAY-1005); (f) non-steroidal antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and
- 10 tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac), fenamic acid derivatives (flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid),
- 15 biphenylcarboxylic acid derivatives (diflunisal and flufenisal), oxicams (isoxicam, piroxicam, sudoxicam and tenoxicam), salicylates (acetyl salicylic acid, sulfasalazine) and the pyrazolones (apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone); (g) cyclooxygenase-2 (COX-2) inhibitors such as
- 20 celecoxib; (h) inhibitors of phosphodiesterase type IV (PDE-IV); (i) antagonists of the chemokine receptors, especially CCR-1, CCR-2, and CCR-3; (j) cholesterol lowering agents such as HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine and
- 25 colestipol), nicotinic acid, fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), and probucol; (k) anti-diabetic agents such as insulin, sulfonylureas, biguanides (metformin), α -glucosidase inhibitors (acarbose) and glitazones (troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like); (l)
- 30 preparations of interferon beta (interferon beta-1a, interferon beta-1b); (m) anticholinergic agents such as muscarinic antagonists (ipratropium bromide); (n) other compounds such as 5-aminosalicylic acid and prodrugs thereof, antimetabolites such as azathioprine and 6-mercaptopurine, and cytotoxic cancer chemotherapeutic agents.

The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is
5 combined with an NSAID the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective
10 dose of each active ingredient should be used.

Compounds of Formula I may be prepared via the schemes outlined below. Reaction conditions are proposed to accomplish the chemical conversions that are outlined. However, one skilled in the art of organic synthesis may find other conditions that are satisfactory for
15 accomplishing the conversions that are suggested.

The central piperidine scaffold may be prepared as outlined in Scheme 1 (for some examples of this sequence see *Bioorganic and Medicinal Chemical Letters* 7 (19), 2531, 1994). The commercially available bis-2-chloroethyl amine hydrochloride A is protected at
20 nitrogen by introduction of a protecting group such as benzyl, methyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (Cbz) in a manner known to one skilled in the art to give B. Generation of the anion of a synthon C with at least 2 equivalents of a base such as lithium diisopropylethyl amide, potassium hydride or sodium hydride followed by addition of B
25 provides piperidines D. D may also be derived from protected piperidine-4-carboxylic acid esters E by deprotonation with a strong base followed by alkylation with an alkyl group substituted with a leaving group. Manipulation of the 'G' group of D in a manner known to one skilled in the art will provide the piperidine F ready for incorporation into
30 compounds of Formula 1. It may be necessary to adjust the protecting group of the piperidine nitrogen, for example to FMOC (fluorenylmethylcarbonyl) for solid phase synthesis, this is well established for one skilled in the art.

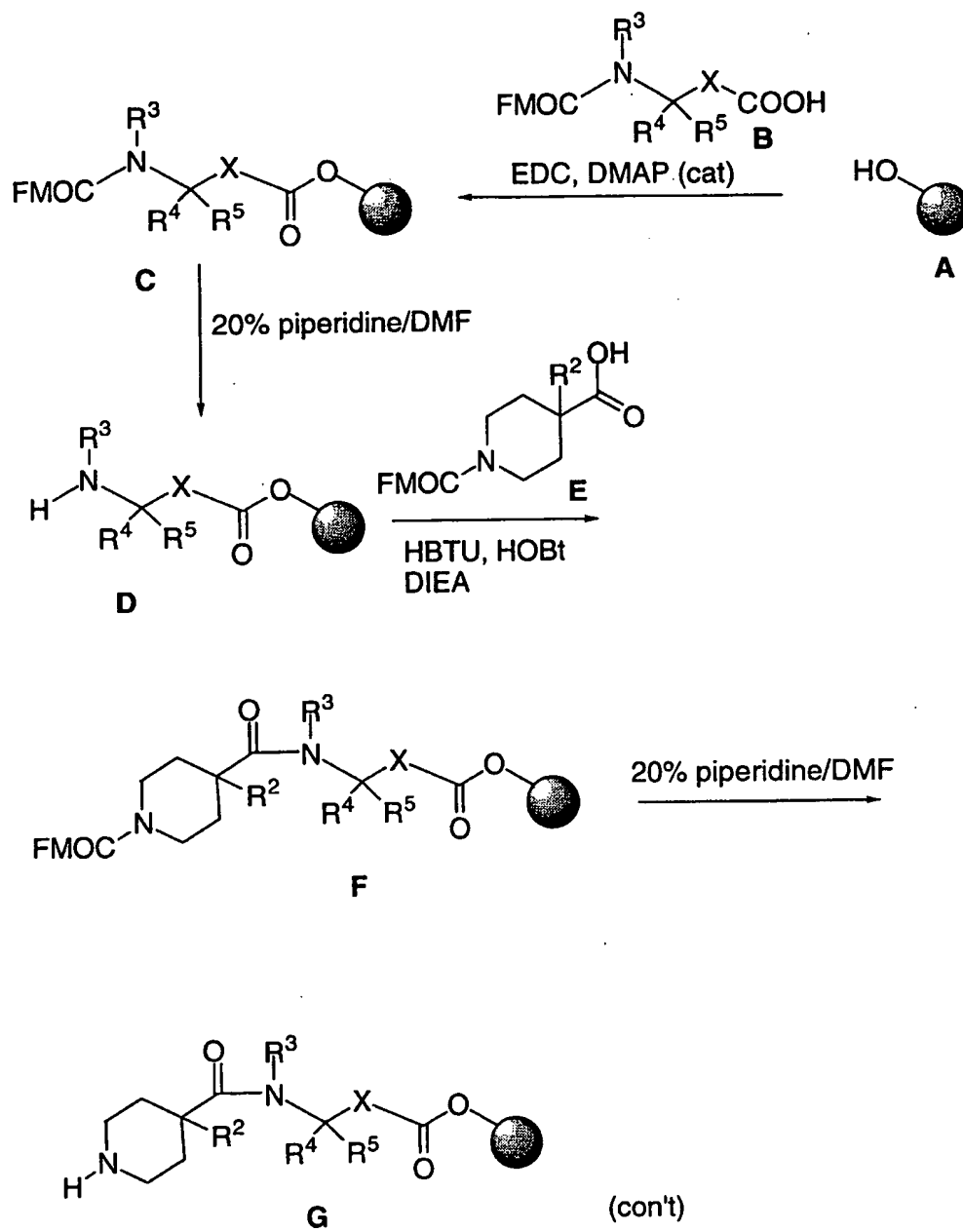
Scheme 1



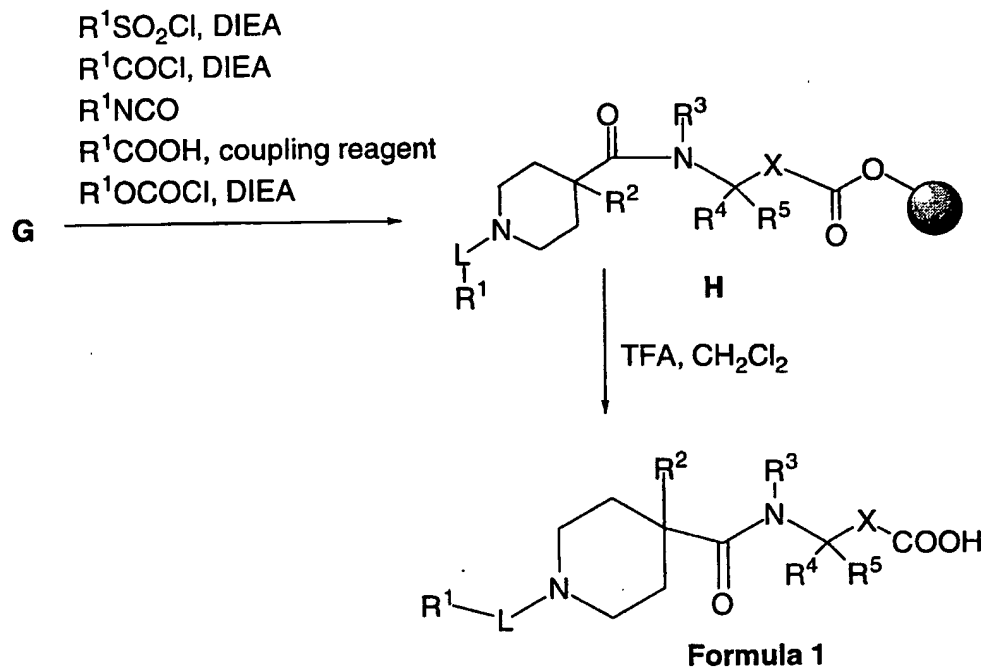
- Compounds of the present invention may be prepared by procedures illustrated in the accompanying schemes. In the first method (Scheme 2), a resin-based synthetic strategy is outlined where the resin employed is represented by the ball (●) A. An N-Fmoc-protected amino acid derivative **B** (Fmoc = fluorenylmethoxycarbonyl) is loaded on to the appropriate hydroxyl-containing resin using

- dicyclohexylcarbodiimide (DCC) or EDC and catalytic amount of dimethylaminopyridine in dimethylformamide (DMF) or methylene chloride (CH_2Cl_2) or a mixture of both to give C. The Fmoc protecting group is removed with piperidine in DMF to yield free amine D. The
- 5 Fmoc-protected piperidine carboxylic acid derivative E is coupled to D employing standard peptide (in this instance, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), HOBT, and N,N-diisopropylethylamine (DIEA) in DMF to yield dipeptoid F. The Fmoc group is removed with piperidine in DMF to yield the free amine
- 10 G. The amine is then derivatized with the appropriate R^1L group by sulfonylation or acylation to give H as indicated on the scheme. The product of this reaction may in itself, be converted further to other R^1 groups by utilization of functional group interconversions well known to one skilled in the art. The final product is removed from the resin with
- 15 strong acid (in this instance, trifluoroacetic acid (TFA) in the presence, or absence (depending on the sensitivity of the product) of thioanisole and dithiane) to yield compounds of the present invention I.

Scheme 2

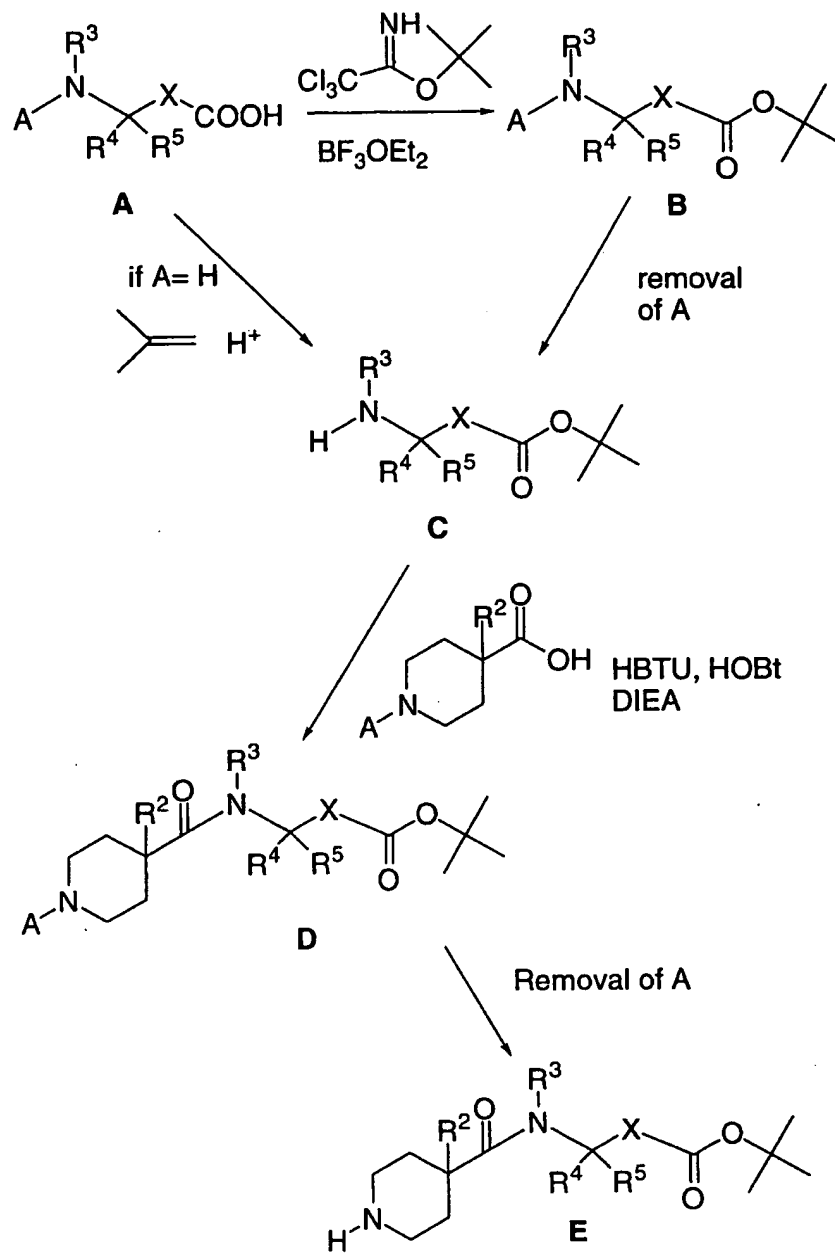


Scheme 2 (con't)



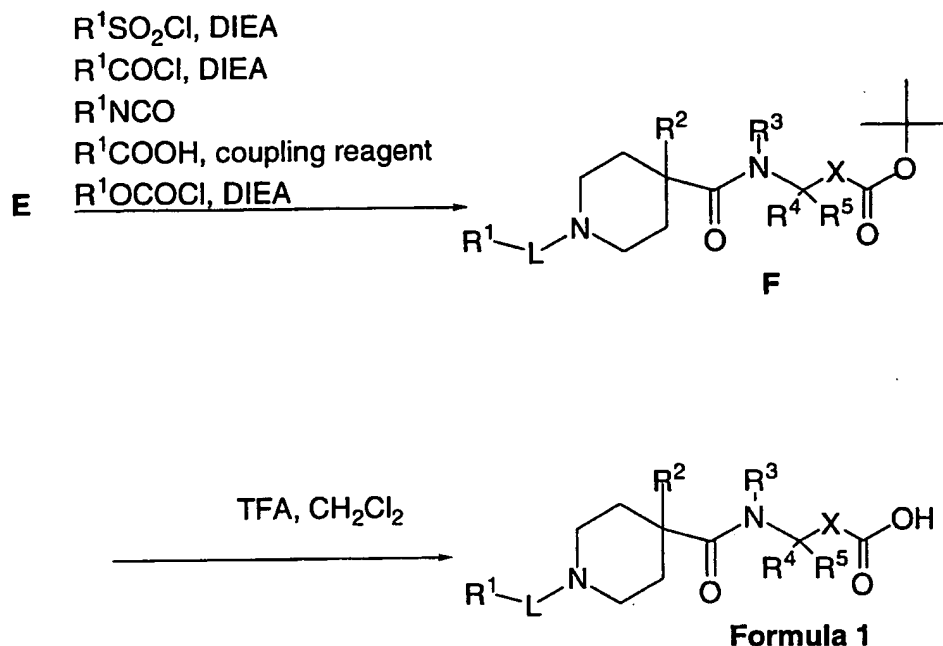
- 5 In the second method (Scheme 3), standard solution phase synthetic methodology is outlined. An N-protected amino acid derivative **A** (Boc = tert-butyloxycarbonyl) is treated with tert-butyl 2,2,2-trichloroacetimidate in the presence of boron trifluoride etherate or isobutylene in the presence of acid (in the case of A=H) to yield tert-butyl ester **B**. **B** is deprotected (in the case of A= Boc, FMOC or Cbz) and the product, **C**, is coupled to an N-protected piperidine carboxylic acid derivative to yield dipeptide **D**. Removal of the N-protecting group A yields **E**. The amine is then derivatized with the appropriate R^1L group by sulfonylation or acylation as indicated on the scheme. The product of
- 10 this reaction may in itself, be converted further to other R^1 groups by utilization of functional group interconversions well know to one skilled in the art. The final product is prepared by acid catalysed removal of the t-butyl ester by treatment with and acid such as TFA.
- 15

Scheme 3



(Con't)

Scheme 3 (con't)



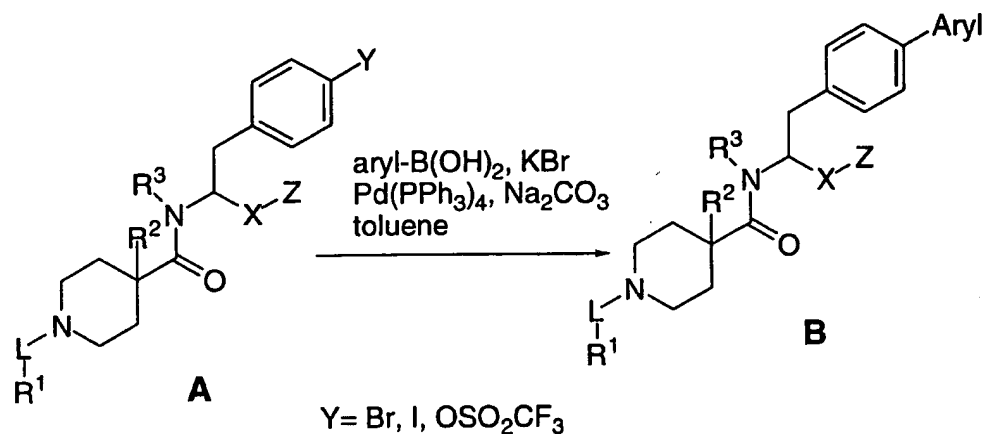
A = CBz, FMOC, BOC

Removal by treatment with: H_2 , 10% Pd/C; 20%
 piperidine/DMF; 1N HCl/ EtOAc respectively.

- Compounds wherein a biaryl moiety is present, for example
- 5 in R^5 , may be prepared as outlined in Scheme 4. The Z group is protected by means known to one skilled in the art. Substituted aryl or heteroaryl boronic acids are coupled to **A** in the presence of a palladium(0) reagent, such as tetrakis(triphenylphosphine)palladium under Suzuki conditions (N. Miyaura *et al.*, *Synth. Commun.*, **1981**, *11*, 513-519) to yield **B**
- 10 Tyrosine triflate starting materials are prepared by treatment of the tyrosine analog of **A** with triflic anhydride in pyridine. The Z group protecting group is then removed to give the corresponding compounds of Formula I. If the aryl or heteroaryl boronic acid is not commercially available, but the corresponding bromide or iodide is, then the bromide
- 15 or iodide can be converted into the desired boronic acid by treatment with an alkyllithium reagent in tetrahydrofuran at low temperature followed by addition of trimethyl or triisopropyl borate. Hydrolysis to the boronic

acid can be effected by treatment of the intermediate with aqueous base and then acid. Aryl boronates which may also be utilized in coupling reactions in place of aryl boronic acids may be prepared by palladium catalyzed boronation of aryl iodides and bromides as described in *J. Org Chem*, **1995**, *60*, 7508-7510.

Scheme 4



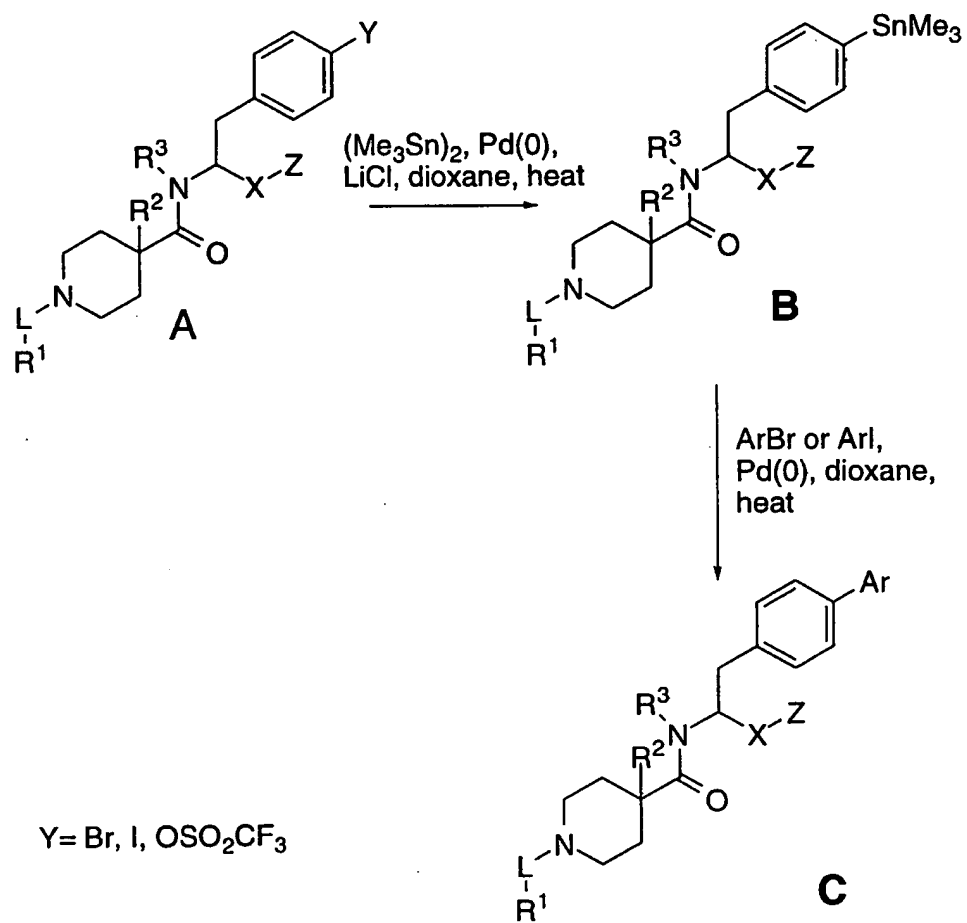
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Alternatively, the aryl coupling reaction may be performed by application of Stille-type carbon-carbon bond forming conditions (Scheme 5). (A.M. Echavarren and J.K. Stille, *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486). The Z group is protected by means known to one skilled in the art. The aryl bromide or iodide intermediate **A** is converted into its trimethyltin derivative **B** using hexamethylditin in the presence of palladium(0) and lithium chloride and then reacted with an appropriately substituted aryl or heteroaryl bromide, iodide, or triflate in the presence of a palladium reagent, such as tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0), in a suitable solvent, such as toluene, dioxane, DMF, or 1-methyl-2-pyrrolidinone, to give intermediate **C**. The protecting group is then removed to give compounds of Formula I. Aryl boronates may also be utilized in coupling reactions in place of aryl stannane. They may be prepared by palladium catalyzed boronation of aryl iodides and bromides

as described in J. Org Chem , 1995, 60, 7508-7510. The resulting boronate may then be coupled to aryl bromide or iodide to provide C

Scheme 5

5



PREPARATION OF 4-PIPERIDINE CARBOXYLIC ACID
INTERMEDIATES.

Preparation 1. N-FMOC-4-phenyl-4-piperidinecarboxylic acid.

5

To a suspension of 3.77 g (10 mmol) of 4-phenyl-4-piperidine-carboxylic acid p-toluenesulfonic acid salt (commercially available) in 31 ml of 10% Na₂CO₃ and 15 ml of dioxane was added at 0°C a solution of 2.58 g (10 mmol) of fluorenylmethyl chloroformate in 20 ml of dioxane
10 dropwise. The reaction mixture was stirred for 3 hours, diluted with 50 ml of water and extracted with EtOAc (3 x 20 ml). The aqueous phase was acidified with conc HCl while stirring vigorously in an ice bath. The resulting solid was collected by filtration, washed with water and dried in vacuo to provide the title compound. ¹H-NMR (CDCl₃, 300MHz):
15 1.85 (bm, 2H); 2.50 (bm, 2H); 3.15 (bm, 2H); 3.80-4.10 (m, 2H); 4.25 (t, 1H); 4.5 (d, 2H); 7.25-7.50 (m, 9H); 7.59 (d, 2H); 7.80 (d, 2H).

Preparation 2. N-FMOC-4-n-butyl-4-piperidinecarboxylic acid.

20 Step A. Preparation of of ethyl N-BOC-4-piperidinecarboxylate

To a mixture of ethyl 4-piperidinecarboxylate (15.7 g, 0.1 mol), 4.8 g (0.11 mmol) sodium hydroxide in 100 ml of THF was added dropwise with stirring a solution of 26.1 g (0.11 mol) of BOC anhydride in 42.5 ml of THF at such a rate so as to prevent reflux. The reaction
25 mixture was stirred at room temperature over night, poured into 200 ml of water and extracted with EtOAc (3 x 150 ml). The combined organic phase was washed with 1N HCl (3 x 75 ml); saturated sodium bicarbonate solution (2 x 75 mL) and brine (1 x 100 ml). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo to give
30 an oil. ¹H-NMR (CDCl₃, 300MHz): 1.75 (t, 3H); 1.92 (s, 9H); 1.62 (m, 2H); 1.87 (bd, 2H); 2.41 (m, 1H); 2.82 (bt, 2H); 4.0 (bm, 2H); 4.112 (q, 2H).

Step B. Preparation of ethyl N-BOC-4-n-butyl-4-piperidine-carboxylate

To a solution of 0.88 g (8.6 mmol) of diisopropylethylamine in 30 ml of THF at 0°C under N₂ was added dropwise 3.52 ml (8.6 mmol) of a solution of 2.5N butyl lithium in hexanes. The solution was stirred for 15 minutes, cooled to -78°C and treated with a solution of ethyl N-BOC-4-piperidinecarboxylate (2.0 g, 8.0 mmol) in 8 ml of THF. The solution was stirred for 1 hour and then 2.16 g (8.4 mmol) of n-butyl iodide was added and the reaction mixture was allowed to warm to room temperature and was stirred over night. The solution was diluted with 100 ml of EtOAc and washed with 1N HCl (3 x 20 ml); saturated sodium bicarbonate solution (2 x 20 mL) and brine (1 x 20 ml). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 10% EtOAc/hexanes to give the desired product. ¹H-NMR (CDCl₃, 400MHz): 0.86 (t, 3H); 1.25 (t, 3H); 1.93 (s, 9H); 1.1-1.8 (m, 8H); 2.08 (bd, 2H); 2.85 9bt, 2H); 3.85 (bd, 2H); 4.16 (q, 2H).

Step C. Preparation of N-BOC-4-n-butyl-4-piperidinecarboxylic acid.

1.5 g (5 mmol) of the product of Step B was heated at 70°C over night in a mixture of 5 ml of 5M NaOH in water (25 mmol) and 5 ml of EtOH. The reaction mixture was concentrated in vacuo and the aqueous residue was washed with ether. The aqueous phase was acidified with 2N HCl and extracted with EtOAc. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo to provide the desired product. ¹H-NMR (CDCl₃, 400MHz): 0.89 (t, 3H); 1.2 - 1.6 (m, 8H); 1.44 (s, 9H); 2.08 (bd, 2H); 2.94 (dt, 2H); 3.86 (bd, 2H).

Step D. Preparation of N-FMOC-4-n-butyl-4-piperidinecarboxylic acid.

1.11 g (4.4 mmol) of the product of Step C was stirred at room temperature in 20 ml of 50% TFA/CH₂Cl₂ for 2 hours. The reaction mixture was concentrated in vacuo. The crude product was then committed to the reaction conditions described in Preparation 1 in the

case of N-FMOC-4-phenyl-4-piperidinecarboxylic acid to give the product as a white solid. ¹H-NMR (CD₃OD, 400MHz): 0.86 (t, 3H); 1.15-1.32 (m, 6H); 1.48 (m, 2H); 2.03 (bt, 2H); 2.91 (bm, 2H); 3.75 (bd, 1H); 3.89 (bd, 1H); 4.20 (t, 1H); 4.42 (m, 2H); 7.29 (t, 2H); 7.36 (t, 2H); 7.54 (t, 2H); 7.82 (d, 2H).

5

Preparation 3. Preparation of N-FMOC-4-methyl-4-piperidinecarboxylic acid

- Step A. Ethyl N-BOC-4-methyl-4-piperidinecarboxylate was prepared as described in Step B of Preparation 2 using iodomethane as the alkylating agent. ¹H-NMR (CDCl₃, 400Mhz): 1.18 (s, 3H); 1.25 (d,t, 3H); 1.31 (dt, 2H); 1.42 (s, 9H); 2.03 (bd, 2H); 2.95 (dt, 2H); 3.72 (m, 2H); 4.14 (q, 2H).
- 15 Step B. N-BOC-4-methyl-4-piperidinecarboxylic acid was prepared as described in Step C of Preparation 2 using the product of Step A. ¹H-NMR (CDCl₃, 400MHz): 1.25 (s, 3H); 1.39 (m, 2H); 1.45 (s, 9H); 2.05 (bd, 2H); 3.05 (dt, 2H); 3.78 (bdt, 2H).
- 20 Step C. Preparation of N-FMOC-4-methyl-4-piperidinecarboxylic acid was prepared as described in Step D of Preparation 2 utilizing the product of Step B as starting material, except as follows. After stirring the reaction mixture overnight in the presence of FMOCCl the mixture was concentrated in vacuo to remove dioxane. The aqueous phase was
- 25 diluted with water and extracted with ether. The desired product was extracted into the ether phase (salt is soluble in ether). The combined ether and aqueous phase were acidified and extracted with ether. The combined ethereal phases were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash
- 30 chromatography over silica gel eluting with 5%MeOH/CH₂Cl₂ to give the desired product. ¹H-NMR (CDCl₃, 400Mhz): 1.22 (s, 3H); 1.40 (bm, 2H); 2.02 (bs, 2H); 3.05 (bs, 2H); 3.75 and 3.85 (bs, 1H); 4.21 (t, 1H); 4.41 (d, 2H); 7.29 (t, 2H); 7.38 (t, 2H); 7.55 (d, 2H); 7.75 (d, 2H).

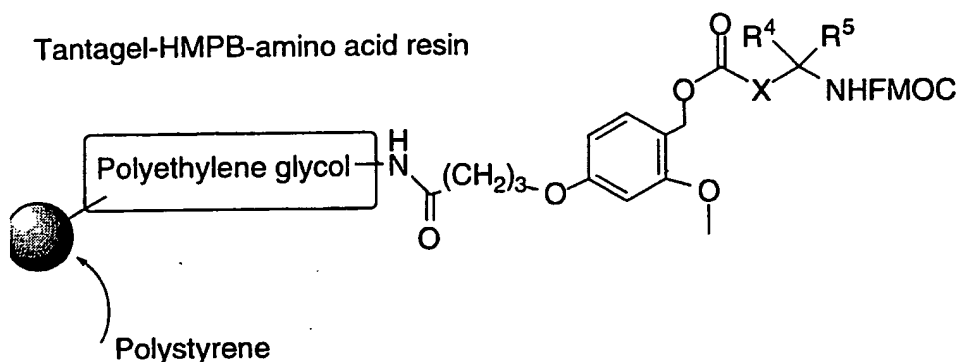
Preparation 4. Preparation of N-FMOC-4-(4-fluorobenzyl)-4-piperidinecarboxylic acid

- Step A. Ethyl N-BOC-4-(4-fluorobenzyl)-4-piperidinecarboxylate was prepared as described in Step B of Preparation 2 using 4-bromomethylfluorobenzene as the alkylating agent. ¹H-NMR (CDCl₃, 400MHz): 1.17 (t, 3H); 1.20-1.40 (m, 2H); 2.05 (bd, 2H); 2.76 (s, 2H), 2.72-2.82 (m, 2H); 4.91 (bm, 2H); 4.08 (q, 2H); 6.89-7.00 (m, 4H).
- Step B. N-BOC-4-(4-fluorobenzyl)-4-piperidinecarboxylic acid was prepared as described in Step C of Preparation 2 using the product of Step A. ¹H-NMR (CDCl₃, 400MHz): 1.38-1.46 (m, 2H); 1.42 (s, 9H); 2.03 (bd, 2H); 2.82 (s, 2H); 2.85 (bt, 2H); 3.92 (bd, 2H); 6.93 (t, 2H); 7.04 (dd, 2H).
- Step C. N-FMOC-4-(4-fluorobenzyl)-4-piperidinecarboxylic acid was prepared as described in Step C, Preparation 3 utilizing the product of Step B as starting material. ¹H-NMR (CDCl₃, 400Mhz): Very broad spectrum. Characteristic signals: 2.02 (bs, 2H); 2.80 (s, 2H); 2.90 (bs, 2H); 3.89 (bs, 1H); 4.05 (bs, 1H); 4.21 (t, 1H); 4.42 (d, 2H); 6.95 (t, 2H); 7.05 (m, 2H); 7.30 (t, 2H); 7.39 (t, 2H); 7.55 (d, 2H); 7.75 (d, 2H).

The following examples are provided to more fully illustrate the invention and are not to be construed as limiting the scope of the invention in any manner.

GENERAL PROCEDURE FOR THE SOLID-PHASE SYNTHESIS OF COMPOUNDS OF FORMULA I.

- Step A. Loading of N-Fmoc-amino acid derivatives onto resins. N-Fmoc-amino acids were loaded onto TantaGel-HMPB-amino acid resin to provide:



The resin was prepared in the following fashion: 25 grams of Tantagel amine resin (commercially available) was swollen in methylene chloride (150 ml). To this mixture was added 3.74 g of 4-hydroxymethyl-3-methoxy-phenoxybutyric acid (commercially available), 2.1 g of N-hydroxybenzotriazole (HOBt) and 1.88 g of diisopropyl carbodiimide. The mixture was stirred over night at room temperature, filtered and the residue was washed with methylene chloride (3 x 150 ml), MeOH (3 x 150 ml), methylene chloride (3 x 150 ml) and ether (3 x 100 ml). The residue was dried in vacuo to give the handle derivatized resin ready for loading with the appropriate amino acid.

The resin (2.0 g, 0.54 mmol) was swollen in 50% THF/CH₂Cl₂ and suspended in 5 ml of the same solvent. 5 mg of dimethylaminopyridine (DMAP) was added followed by 1.0 mmol of the amino acid N-protected with the fluorenylmethoxycarbamate (Fmoc) group. EDC (1.0 mmol) was added and the mixture was agitated over night. The mixture was filtered and then resubmitted to the same conditions for 4 hours. The mixture was filtered and the residue was washed (3 x 10 ml 50% THF/CH₂Cl₂), 3 x 10 ml CH₂Cl₂, 3 x 10 ml MeOH, 3 x 10 ml CH₂Cl₂, 2 x 10 ml ether) and dried in vacuo to give the desired product.

Step B. Deprotection of the N-Fmoc group.

25 The N-Fmoc protecting group was removed from the resin (75 mg , 0.015 mmol) from Step A by treatment with 20% piperidine in dimethylformamide for 30 minutes. Following filtration, the resin was washed sequentially with dimethylformamide (3 times),

dichloromethane (1 time) and dimethylformamide (2 times) and used in the subsequent reaction.

Step C. Coupling of the next N-Fmoc-amino acid derivative

5 A solution of the N-Fmoc-piperidine-4-carboxylic acid (0.06 mmol) in dimethylformamide (1 mL) was mixed with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.75 mmol), 1-N-hydroxybenzotriazole (0.06 mmol) and diisopropylethylamine (0.07 mmol). This solution was transferred to resin from Step B and typically allowed
10 to react for 2 hours. Couplings were monitored by ninhydrin reaction. The coupling mixture was filtered and the resin washed with dimethylformamide (3 times) and used in the subsequent reaction.

Step D. Deprotection of the N-Fmoc group.

15 The N-Fmoc protecting group was removed from the resin from Step C by the procedure described in Step B and used in the subsequent reaction.

Step E. Acylation (or sulfonylation) of the terminal amino group.

20 The desired N-terminal capping reagent (sulfonylchloride or acylchloride) (0.06 mol) was dissolved in 50% CH₂Cl₂/THF (2 ml), mixed with N,N-diisopropylethylamine(0.8 mmol) and added to the resin from Step D. After agitating over night, the resin was sequentially washed (3 x 3 ml 50% THF/CH₂Cl₂), 3 x 3 ml CH₂Cl₂, 3 x 3 ml MeOH, 3 x
25 3 ml CH₂Cl₂

Step F. Acylation with carboxylic acid

A solution of the next carboxylic acid (0.06 mmol) in dimethylformamide (1 mL) was mixed with 2-(1H-benzotriazol-1-yl)-
30 1,1,3,3-tetramethyluronium hexafluorophosphate (0.75 mmol), 1-N-hydroxybenzotriazole(0.06 mmol) and diisopropylethylamine (0.07 mmol). This solution was transferred to resin from Step D and typically allowed to react overnight. The coupling mixture was filtered and the resin

washed with (3 x 3 ml DMF), 3 x 3 ml CH₂Cl₂, 3 x 3 ml MeOH, 3 x 3 ml CH₂Cl₂

Step G. Further modifications of product of Step E and Step F
5 The product of Step E and Step F may be further modified by Fmoc group removal as described above and acylations of the type described in Step E and F using excess amounts of acids, sulfonyl chlorides, isocyanates (in 50% CH₂Cl₂/THF), chloroformates, and acid chlorides. Reactions are always followed by rigorous washing with the
10 reaction solvent and subsequently CH₂Cl₂, MeOH and CH₂Cl₂

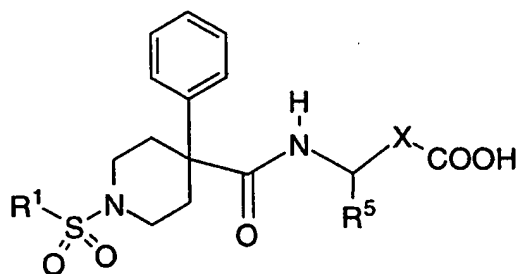
Step F. Cleavage of the desired products from the resins.
The final desired products were cleaved from the resins from Step E-H by mixing with a solution of 5% trifluoroacetic acid in
15 CH₂Cl₂ (3 x 3 ml for 10 minutes each) and filtering. The filtrate was concentrated in vacuo. The residue was dissolved in 50% CH₃CN/H₂O and lyophilised. In the case of t-butyl tyrosine and t-butyl aspartate commercially available SASRIN resins was utilised and 1% trifluoroacetic acid in CH₂Cl₂ (10 x 1 ml for 3 minutes) was used for
20 cleavage. The eluant was run into 20% pyridine in methanol and the mixture was concentrated in vacuo. Purity was assessed by HPLC and molecular ions were obtained by electrospray ionization mass spectrometry to confirm the structure of each compound.

25

EXAMPLES 1-64

The following compounds were prepared by the general procedure described above using the appropriate amino acid derivatives and other reagents. In the case of amides derived from 2-methyl-
30 phenylureaphenylacetic acid, the acid used for coupling, 2-methyl-phenylureaphenylacetic acid, was prepared as in International Patent Application WO 96/22966. In the lists below the carbon atom to which R₅ is attached has the same stereo configuration as the corresponding carbon atom of the L-amino acid starting material, except when marked

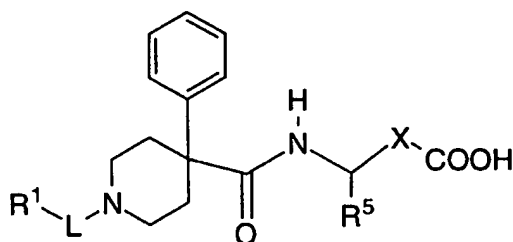
with *, the starting amino acid is a dl mixture, and when marked with #, the starting amino acid is a D-amino acid.



5

| Ex. | X | R ¹ | R ⁵ | Obs. FAB-MS |
|-----|-----------------|----------------------------------|------------------------|-----------------------------------------------------|
| 1 | - | 3,5-diCl-Ph | n-butyl | 544 (M ⁺ +18) |
| 2 | - | 3,5-diCl-Ph | benzyl | 578 (M ⁺ +18) |
| 3 | - | 3,5-diCl-Ph | phenyl* | 564 (M ⁺ +18) |
| 4 | - | 3,5-diCl-Ph | (4-biphenyl) methyl | 654 (M ⁺ +18) |
| 5 | CH ₂ | 3,5-diCl-Ph | methyl* | 516 (M ⁺ +18) |
| 6 | CH ₂ | 3,5-diCl-Ph | benzyl* | 592 (M ⁺ +18) |
| 7 | CH ₂ | 3,5-diCl-Ph | isopropyl* | 558 (M ⁺ +18) |
| 8 | CH ₂ | 3,5-diCl-Ph | phenyl* | 578 (M ⁺ +18) |
| 9 | CHMe* | 3,5-diCl-Ph | H | 516 (M ⁺ +18) |
| 10 | - | n-C ₄ H ₉ | benzyl | 473 (M ⁺ +1) 490 (M ⁺ +18) |
| 11 | - | n-C ₈ H ₁₇ | benzyl | 546 (M ⁺ +18) |
| 12 | - | Ph | benzyl | 510 (M ⁺ +18) |
| 13 | - | 4-F-Ph | benzyl | 511 (M ⁺ +1) 528 (M ⁺ +18) |
| 14 | - | 3,5-diCl-Ph | benzyl | 578 (M ⁺ +18) |
| 15 | - | 4-CH ₃ O-Ph | benzyl | 523 (M ⁺ +1) 540 (M ⁺ +18) |
| 16 | - | 4-CH ₃ C(O)NH-Ph | benzyl | 550 (M ⁺ +1) 567 (M ⁺ +18) |
| 17 | - | 4-CF ₃ O-Ph | benzyl | 577 (M ⁺ +1) 594 (M ⁺ +18) |

| | | | | |
|----|---|----------------------------|--------|-----------------------------------------------------|
| 18 | - | 3-CF ₃ -Ph | benzyl | 561 (M ⁺ +1) 578 (M ⁺ +18) |
| 19 | - | 3,5-di(CF ₃)Ph | benzyl | 629 (M ⁺ +1) |
| 20 | - | 3-CH ₃ -Ph | benzyl | 524 (M ⁺ +18) |
| 21 | - | 3-CN-Ph | benzyl | 518 (M ⁺ +1) 535 (M ⁺ +18) |
| 22 | - | 3-Cl-Ph | benzyl | 527 (M ⁺ +1) 544 (M ⁺ +18) |
| 23 | - | 3-F-Ph | benzyl | 528 (M ⁺ +18) |



| Ex | Note | X | R1-L | R5 | Obs. FAB-MS |
|----|------|-----------------|-----------|------------------------|-----------------------------------------------------|
| 24 | - | - | 2-MPUPA** | n-pentyl | 602 (M ⁺ +18) |
| 25 | - | - | 2-MPUPA | benzyl | 636 (M ⁺ +18) |
| 26 | - | - | 2-MPUPA | phenyl* | 622 (M ⁺ +18) |
| 27 | - | - | 2-MPUPA | (4-biphenyl) methyl | 695 |
| 28 | - | CH ₂ | 2-MPUPA | methyl* | 557 (M ⁺ +1) 574 (M ⁺ +18) |
| 29 | - | CH ₂ | 2-MPUPA | benzyl* | 633 (M ⁺ +1) 650 (M ⁺ +18) |
| 30 | - | CH ₂ | 2-MPUPA | isobutyl* | 599 (M ⁺ +1) 616 (M ⁺ +18) |
| 31 | - | CH ₂ | 2-MPUPA | phenyl* | 636 (M ⁺ +18) |
| 32 | - | CHMe* | 2-MPUPA | H | 557 (M ⁺ +1) 574 (M ⁺ +18) |
| 33 | - | - | 2-MPUPA | 4-tBuO-benzyl | 708 (M ⁺ +18) |
| 34 | - | - | 2-MPUPA | methyl | 543 (M ⁺ +1) 560 (M ⁺ +18) |

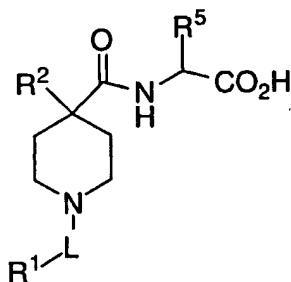
| | | | | | |
|----|---|---|------------------------------------------|------------------------|-----------------------------------------------------|
| 35 | - | - | 2-MPUPA | benzyl# | 636 (M ⁺ +18) |
| 36 | - | - | 2-MPUPA | 4-fluorobenzyl | 637 (M ⁺ +1) 654 (M ⁺ +18) |
| 37 | A | - | 9-fluorenylmethoxy carbonyl | 4-fluorobenzyl | 610 (M ⁺ +18) |
| 38 | B | - | benzoyl | 4-fluorobenzyl | 475 (M ⁺ +1) |
| 39 | C | - | phenylacetyl | 4-fluorobenzyl | 489 (M ⁺ +1) |
| 40 | D | - | phenylcarbamoyl | 4-fluorobenzyl | 490 (M ⁺ +1) |
| 41 | E | - | 4-(benzamido) phenylacetyl | 4-fluorobenzyl | 608 (M ⁺ +1) 625 (M ⁺ +18) |
| 42 | F | - | 4- (phenylacetamido) phenylacetyl | 4-fluorobenzyl | 622 (M ⁺ +1) 639 (M ⁺ +18) |
| 43 | G | - | 4-(2-Me-phenylacet amido)phenylacetyl | 4-fluorobenzyl | 636 (M ⁺ +1) 653 (M ⁺ +18) |
| 44 | H | - | PUPA | 4-fluorobenzyl | 640 (M ⁺ +18) |
| 45 | I | - | 2-MPUPA | 4-fluorobenzyl | 654 (M ⁺ +18) |
| 46 | J | - | 3-MPUPA | 4-fluorobenzyl | 654 (M ⁺ +18) |
| 47 | K | - | 4-MPUPA | 4-fluorobenzyl | 654 (M ⁺ +18) |
| 48 | L | - | 4-(PhOC(O)NH) phenylacetyl | 4-fluorobenzyl | 641 (M ⁺ +18) |
| 49 | - | - | 2-MPUPA | t-BuO-C(O)- methyl | 660 (M ⁺ +18) |
| 50 | - | - | 2-MPUPA | t-BuO- C(O)NH-butyl | 708 (M ⁺ +18) |
| 51 | - | - | 2-MPUPA | t-BuO-methyl | 615 (M ⁺ +1) 632 (M ⁺ +18) |
| 52 | - | - | 2-MPUPA | carboxymethyl | 587 (M ⁺ +1) 604 (M ⁺ +18) |

** 2-MPUPA is 4-(N'-2-methyl-phenylureido)phenylacetyl (see Example 61 for structure); PUPA is phenylureaphenylacetyl

Notes:

Note A: Product of Step A; Note B: Step F with benzoic acid; Note C: Step F with phenylacetic acid; Note D: Step G with phenyl isocyanate; Note E:

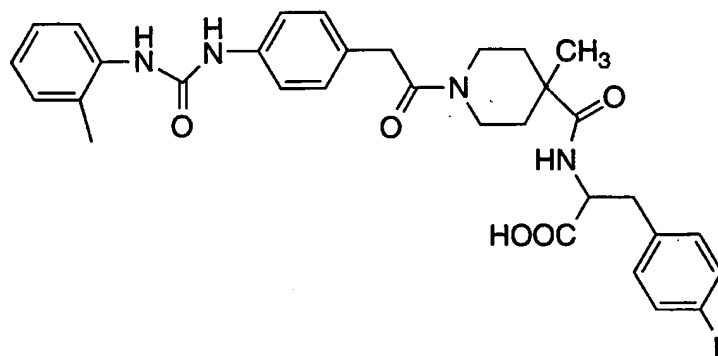
- Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step F with benzoic acid; Note F: Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step F with phenylacetic acid; Note G: Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step F with 2-methylphenylacetic acid; Note H: Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step G with phenylisocyanate; Note I: Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step G with 2-methylphenylisocyanate; Note J: : Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step G with 3-methylphenylisocyanate; Note K: : Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step G with 4-methylphenylisocyanate; Note L: Step F with FMOC-4-aminophenyl acetic acid followed by Step D and Step G with phenylchloroformate.



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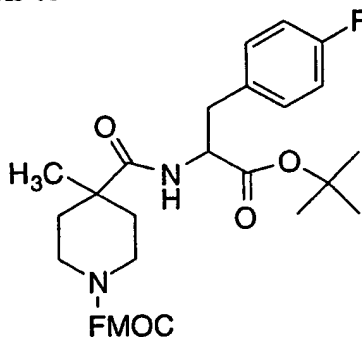
| Ex. | R ² | R ¹ -L | R ⁵ | Obs. FAB-MS |
|-----|-----------------|-----------------------------|--------------------|-----------------------------------------------------|
| 53 | CH ₃ | 2-MPUPA | 4-(tBuO)-benzyl | 629 (M ⁺ +1) 646 (M ⁺ +18) |
| 54 | CH ₃ | 2-MPUPA | t-BuO-C(O)-methyl | 581 (M ⁺ +1) 598 (M ⁺ +18) |
| 55 | CH ₃ | 2-MPUPA | n-butyl | 523 (M ⁺ +1) 540 (M ⁺ +18) |
| 56 | CH ₃ | 2-MPUPA | benzyl | 557 (M ⁺ +1) 574 (M ⁺ +18) |
| 57 | CH ₃ | 2-MPUPA | methyl | 481 (M ⁺ +1) 498 (M ⁺ +18) |
| 58 | CH ₃ | 3,5-diCl-Ph-SO ₂ | (4-biphenyl)methyl | 575 (M ⁺ +1) |

| | | | | |
|----|---------------------------------|---------|-----------------|--------------------------|
| 59 | n-C ₄ H ₉ | 2-MPUPA | 4-fluorobenzyl | 617 (M ⁺ +1) |
| | | | | 634 (M ⁺ +18) |
| 60 | 4-F-Ph-CH ₂ | 2-MPUPA | 4-fluorobenzyl | 669 (M ⁺ +1) |
| | | | | 686 (M ⁺ +18) |
| 61 | CH ₃ | 2-MPUPA | 4-hydroxybenzyl | 573 (M ⁺ +1) |
| 62 | CH ₃ | 2-MPUPA | carboxymethyl | 525 (M ⁺ +1) |

EXAMPLE 63

5 N-(4-methyl-1-(4-(N'-2-methyl-phenylureido)phenylacetyl)piperidinyl-4-carbonyl)-(L)-4-fluorophenylalanine

Step A. Preparation of



10

0.16 g (0.42 mmol) of N-FMOC-4-methyl-4-piperidine-carboxylic acid, 0.1 g (0.42 mmol) of L-4-fluorophenylalanine t-butyl ester, 0.24g (0.63 mmol) HBTU and 85 mg (0.63 mmol) of N-hydroxybenzotriazole hydrate were combined in 5 ml of dry DMF. The mixture was treated with 0.36 ml (2.09 mmol) of diisopropylethylamine. The reaction mixture was stirred for 2 hours, diluted with 50 ml of EtOAc

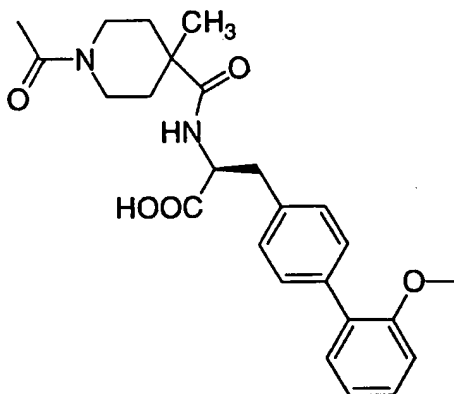
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and washed with 1N HCl (2 x 15 ml), saturated sodium bicarbonate solution (2 x 15 ml) and brine (1 x 15 ml). The organic phase was dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with

- 5 50%EtOAc/hexanes to provide the product. $^1\text{H-NMR}$ (CDCl_3 , 400MHz): 1.12 (s, 3H); 1.2-1.5 (bm, 2H); 1.41 (s, 9H); 1.87 (m, 2H); 3.0-3.20 (m, 5H); 3.6 (vbm, 2H); 4.20 (t, 1H); 4.40 (d, 2H); 4.71 (q, 1H); 6.0 (d, 1H); 6.95 (t, 2H); 7.06 (m, 2H); 7.28 (t, 2H); 7.37 (t, 2H); 7.53 (d, 2H); 7.72 (d, 2H).

10 Step B. Preparation of Title Compound

- The product of Step A (0.19 mmol) was treated with 10 ml of 1:1 CH_2Cl_2 : Et_2NH and stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo. The residue was then combined in 5 ml of DMF with 56.5 mg (0.23 mmol) of 4-(2-methyl-
15 phenylureido)phenylacetic acid, 0.11g (0.29 mmol) of HBTU, 0.04 g (0.29 mmol) N-hydroxybenzotriazole hydrate and lastly, 0.1 ml (0.57 mmol) of diisopropylethylamine. The reaction mixture was stirred at room temperature over night, diluted with 50 ml of EtOAc and washed with 1N HCl (2 x 15 ml), saturated sodium bicarbonate solution (2 x 15 ml) and
20 brine (1 x 15 ml). The organic phase was dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 50%EtOAc/hexanes to provide the intermediate t-butyl ester. The material was stirred with 1:1 TFA/ CH_2Cl_2 over night, concentrated in vacuo and purified by
25 preparatory thin layer chromatography eluting with 10% MeOH/ CH_2Cl_2 1% HOAc to give the desired product as a glass. The $^1\text{H-NMR}$ was very broad and not useful for characterization. The material was pure by HPLC (C-8 column eluting with a gradient of 10-90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ buffered with 0.1% TFA). FABMS calculated for $\text{C}_{32}\text{H}_{25}\text{N}_4\text{O}_5\text{F}_1$
30 calculated: 574; Observed: 575 ($\text{M}^+ + 1$), 592 ($\text{M}^+ + 18$).

EXAMPLE 64N-(1-acetyl-4-methyl-piperidinyl-4-carbonyl)-(L)-4-fluorophenylalanine

5

Step A

Preparation of (S)-2'-methoxybiphenylalanine t-butyl ester hydrochloride

To a solution of 15g (51 mmol) of (L)-4-iodophenylalanine in
10 100 ml of diglyme and 15 ml of concentrated H₂SO₄ was added 30 ml of
condensed isobutylene. The vessel was agitated overnight and the crude
product was diluted with 100 ml of ethyl acetate. The solution was added
to excess sodium hydroxide solution while maintaining the temperature
below 30°C. A white precipitate formed which dissolved upon addition of
15 sodium hydroxide solution. The resulting mixture was filtered and the
aqueous phase was extracted with ethyl acetate. The combined extracts
were washed with brine and dried over anhydrous magnesium sulfate.
The mixture was filtered and concentrated in vacuo to give a solution of
the product in diglyme. The solution was diluted with 200 ml of ether
20 and was treated with excess 1N HCl in ether with rapid stirring. The
resulting precipitate was collected and dried in vacuo after washing
with ether. A white solid (9.01 g) was collected of 4-iodophenylalanine t-
butyl ester hydrochloride. To a suspension of 7.5 g (0.019 m) of 4-iodo-
phenylalanine t-butyl ester in 100 ml of dichloromethane was added 2.52
25 g 0.019 m of diisopropyl ethyl amine followed by 4.14 g of di-t-butyl-
dicarbonate. The reaction mixture was stirred over night at room

temperature, washed with 1N HCl (2 x 25 ml), water (2 x 25 ml), saturated NaHCO₃ (1 x 25 ml), brine (1 x 25 ml) and was dried over MgSO₄. The mixture was filtered and concentrated in vacuo to give N-Boc-(L)-4-iodophenylalanine t-butyl ester as a gum 8.8 g (100% yield). 300
5 MHz ¹H NMR (CDCl₃): 1.39 (s, 18H); 2.98 (AB, 2H); 4.4 (dd, 2H); 5.0 bd, 1H); 6.92 (d, 2H); 7.62 (d, 2H).

7.97 g (0.018 m) of N-Boc-(L)-4-iodophenylalanine t-butyl ester was dissolved in 160 ml of 2:1 toluene:ethanol. To this solution was added 2.99 g (0.0198 m) 2-methoxyphenylboronic acid, 0.69 g of
10 tetrakis(triphenylphosphine) palladium (0) and 22.7 ml (0.45 m) of 2.0 M sodium carbonate in water. The reaction mixture was degassed three times and then heated at 90°C for 90 minutes at which time the reaction mixture was black. The mixture was diluted with 300 ml of ethyl acetate and was washed with water (3 x 150 ml) and brine (2 x 100 ml) and was
15 dried over MgSO₄. The mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 10% EtOAc/hexanes to give 6.89 g (88% yield) of N-Boc-(L)-2'-methoxybiphenylalanine t-butyl ester as a white solid. 300 MHz ¹H NMR (CDCl₃): 1.45 (s, 18H); 3.10 (d, 2H); 3.80 (s, 3H); 4.5 (dd, 2H); 5.1 bd, 1H);
20 7.0 (m, 2H); 7.22 (d, 2H); 7.30 (d, 2H); 7.49 (d, 2H); 7.62 (d, 2H).

To a solution of 4.85 g (0.0113 m) of N-Boc-(L)-2'-methoxybiphenylalanine t-butyl ester in 100 ml of t-butyl acetate was added 5.53 g (0.056 m) of concentrated sulfuric acid. The solution was stirred at room temperature for 2 hours and then carefully neutralised by addition of
25 saturated aqueous NaHCO₃ solution. The solution was washed with NaHCO₃ solution, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in 50 ml of ether and treated with anhydrous HCl gas with stirring to give a white precipitate. The solid was collected by filtration, washed with ether and dried in vacuo to give the desired
30 product. 300 MHz ¹H NMR (CD₃OD): 1.45 (s, 9H); 3.20 (d, 2H); 3.79 (s, 3H); 4.21 (t, 1H); 7.03 (m, 2H); 7.28 (m, 2H); 7.31 (d, 2H); 7.50 (d, 2H).

Step B. Preparation of N-acetyl-4-(methyl)-piperidine-4-carboxylic acid.

To a solution of 140 mg (0.68 mmol) ethyl 4-methyl-
5 piperidine-4-carboxylate hydrochloride (the product of treatment of ethyl
N-BOC-4-methyl-piperidine-4-carboxylate (Preparation 3, Step A) with
HCl/EtOAc and concentrating in vacuo) in 4 ml of CH_2Cl_2 was added 260
mg (2 mmol) of diisopropylethyl amine followed by 70 mg (0.68 mmol) of
10 acetic anhydride. The reaction was diluted with ethyl acetate after one
hour and was washed with water and saturated sodium bicarbonate
solution and was dried over MgSO_4 . The mixture was filtered and
concentrated in vacuo. The residue was dissolved in 5 ml of methanol
and was treated with excess 2N NaOH solution. The solution was stirred
15 over night at room temperature, concentrated in vacuo to remove
methanol and was extracted with ether. The aqueous phase was
acidified with 1N HCl solution and was extracted with ethyl acetate to
provide, after drying over MgSO_4 , 48.8 mg of the desired product.

Step C. Preparation of the title compound

20 47.2 mg (0.13 mmol) of the product of Step A was combined
with 24 mg (0.13 mmol) of the product of Step B, 74 mg (0.2 mmol) of
HBTU, 26 mg (0.2 mmol) of HOBT and 50 mg (0.4 mmol) of diisopropyl
ethyl amine in 2 ml of methylene chloride. The reaction mixture was
stirred over night at room temperature. The solution was diluted with
25 ethyl acetate (10 ml) and was washed with 1N HCl (2 x 3 ml), saturated
 NaHCO_3 (2 x 5 ml), water (1 x 5 ml) and brine (1 x 5 ml) was dried over
 MgSO_4 . The mixture was filtered and concentrated in vacuo and the
residue was purified by preparatory thin layer chromatography over
silica gel. The product was treated with 3 ml of 1:1 TFA/ CH_2Cl_2 for 4
30 hours and concentrated in vacuo to provide the title compound. 300 MHz
 ^1H NMR (CD_3OD): two rotomers, characteristic signals: 1.08 and 1.09 (s,
3H total); 1.20-1.35 (m, 4H); 1.89 and 1.92 (s, 3H total); 3.75 (s, 3H); 6.95-
7.05 (m, 2H); 7.18-7.30 (m, 3H); 7.40 (t, 2H); 7.80 (t, 1H). FABMS: Calc.
 $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_5$; 438; Obs.: 439

EXAMPLE 65

Inhibition of VLA-4 Dependent Adhesion to BSA-CS-1 Conjugate

5

Step A. Preparation of CS-1 Coated Plates.

Untreated 96 well polystyrene flat bottom plates were coated with bovine serum albumin (BSA; 20 µg/ml) for 2 hours at room temperature and washed twice with phosphate buffered saline (PBS).

- 10 The albumin coating was next derivatized with 10 µg/ml 3-(2-pyridyldithio) propionic acid N-hydroxysuccinimide ester (SPDP), a heterobifunctional crosslinker, for 30 minutes at room temperature and washed twice with PBS. The CS-1 peptide (Cys-Leu-His-Gly-Pro-Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr), which was synthesized by conventional solid
- 15 phase chemistry and purified by reverse phase HPLC, was next added to the derivatized BSA at a concentration of 2.5 µg/ml and allowed to react for 2 hours at room temperature. The plates were washed twice with PBS and stored at 4°C.

20 Step B. Preparation of Fluorescently Labeled Jurkat Cells.

Jurkat cells, clone E6-1, obtained from the American Type Culture Collection (Rockville, MD; cat # ATCC TIB-152) were grown and maintained in RPMI-1640 culture medium containing 10% fetal calf serum (FCS), 50 units/ml penicillin, 50 µg/ml streptomycin and 2 mM

- 25 glutamine. Fluorescence activated cell sorter analysis with specific monoclonal antibodies confirmed that the cells expressed both the α4 and β1 chains of VLA-4. The cells were centrifuged at 400xg for five minutes and washed twice with PBS. The cells were incubated at a concentration of 2×10^6 cells/ml in PBS containing a 1 µM concentration
- 30 of a fluorogenic esterase substrate (2', 7'-bis-(2-carboxyethyl)-5-(and -6)-carboxyfluorescein, acetoxymethyl ester; BCECF-AM; Molecular Probes Inc., Eugene, Oregon; catalog #B-1150) for 30-60 minutes at 37°C in a 5% CO₂/air incubator. The fluorescently labeled Jurkat cells were washed

two times in PBS and resuspended in RPMI containing 0.25% BSA at a final concentration of 2.0×10^6 cells/ml.

StepC. Assay Procedure.

5 Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μ M. Three μ L of diluted compound, or vehicle alone, were premixed with 300 μ L of cell suspension in 96-well polystyrene plates with round bottom wells. 100 μ L
10 aliquots of the cell /compound mixture were then transferred in duplicate to CS-1 coated wells. The cells were next incubated for 30 minutes at room temperature. The non-adherent cells were removed by two gentle washings with PBS. The remaining adherent cells were quantitated by reading the plates on a Cytofluor II fluorescence plate
15 reader (Perseptive Biosystems Inc., Framingham, MA; excitation and emission filter settings were 485 nm and 530 nm, respectively). Control wells containing vehicle alone were used to determine the level of cell adhesion corresponding to 0% inhibition. Control wells coated with BSA and crosslinker (no CS-1 peptide) were used to determine the level of cell
20 adhesion corresponding to 100% inhibition. Cell adhesion to wells coated with BSA and crosslinker was usually less than 5% of that observed to CS-1 coated wells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

25

EXAMPLE 66

Antagonism of VLA-4 Dependent Binding to VCAM-Ig Fusion Protein.

30 Step A. Preparation of VCAM-Ig.

The signal peptide as well as domains 1 and 2 of human VCAM (GenBank Accession no. M30257) were amplified by PCR using the human VCAM cDNA (R & D Systems) as template and the following

primer sequences: 3'-PCR primer: 5'-AATTATAATTTGATCAACTTAC
CTGTCAATTCTTTTACAGCCTGCC-3';

5'-PCR primer:

5'-ATAGGAATTCCAGCTGCCACCATGCCTGGGAAGATGGTCG-3'.

- 5 The 5'-PCR primer contained EcoRI and PvuII restriction
sites followed by a Kozak consensus sequence (CCACC) proximal to the
initiator methionine ATG. The 3'-PCR primer contained a BclI site and
a splice donor sequence. PCR was performed for 30 cycles using the
following parameters: 1 min. at 94°C, 2 min. at 55°C, and 2 min. at
10 72°C. The amplified region encoded the following sequence of human
VCAM-1:
MPGKMVVILGASNILWIMFAASQAFKIETTPESRYLAQIGDSVSLTC
STTGCESPFFSWRTQIDSPLNGKVTNEGTTSTLTMNPVSFGNEHSYLC
TATCESRKLEKGIQVEIYSFPKDPEIHLSGPLEAGKPITVKCSVADVY
15 PFDRLEIDLLKGDHLMKSQEFLEADRSLETKSLEVTFTPTVIEDIGKV
LVCRAKLHIDEMDSVPTVRQAVKEL. The resulting PCR product of
650 bp was digested with EcoRI and BclI and ligated to expression vector
pIg-Tail (R & D Systems, Minneapolis, MN) digested with EcoRI and
BamHI. The pIg-Tail vector contains the genomic fragment which
20 encodes the hinge region, CH2 and CH3 of human IgG1 (GenBank
Accession no. Z17370). The DNA sequence of the resulting VCAM
fragment was verified using Sequenase (US Biochemical, Cleveland,
OH). The fragment encoding the entire VCAM-Ig fusion was
subsequently excised from pIg-Tail with EcoRI and NotI and ligated to
25 pCI-neo (Promega, Madison, WI) digested with EcoRI and NotI. The
resulting vector, designated pCI-neo/VCAM-Ig was transfected into
CHO-K1 (ATCC CCL 61) cells using calcium-phosphate DNA
precipitation (Specialty Media, Lavalette, NJ). Stable VCAM-Ig
producing clones were selected according to standard protocols using
30 0.2-0.8 mg/ml active G418 (Gibco, Grand Island, NY), expanded, and cell
supernatants were screened for their ability to mediate Jurkat adhesion
to wells previously coated with 1.5 µg/ml (total protein) goat anti-human
IgG (Sigma, St. Louis, MO). A positive CHO-K1/VCAM-Ig clone was
subsequently adapted to CHO-SFM serum-free media (Gibco) and

maintained under selection for stable expression of VCAM-Ig. VCAM-Ig was purified from crude culture supernatants by affinity chromatography on Protein A/G Sepharose (Pierce, Rockford, IL) according to the manufacturer's instructions and desalted into 50 mM sodium phosphate buffer, pH 7.6, by ultrafiltration on a YM-30 membrane (Amicon, Beverly, MA).

Step B. Preparation of ^{125}I -VCAM-Ig.

VCAM-Ig was labeled to a specific radioactivity greater than 1000 Ci/mmol with ^{125}I -Bolton Hunter reagent (New England Nuclear, Boston, MA; cat # NEX120-0142) according to the manufacturer's instructions. The labeled protein was separated from unincorporated isotope by means of a calibrated HPLC gel filtration column (G2000SW; 7.5 x 600 mm; Tosoh, Japan) using uv and radiometric detection.

Step C. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μM . Jurkat cells were centrifuged at 400xg for five minutes and resuspended in binding buffer (25 mM HEPES, 150 mM NaCl, 3 mM KCl, 2 mM glucose, 0.1% bovine serum albumin, pH 7.4). The cells were centrifuged again and resuspended in binding buffer supplemented with MnCl_2 at a final concentration of 1 mM. Compounds were assayed in Millipore MHVB multiscreen plates (cat# MHVBN4550, Millipore Corp., MA) by making the following additions to duplicate wells: (i) 200 μL of binding buffer containing 1 mM MnCl_2 ; (ii) 20 μL of ^{125}I -VCAM-Ig in binding buffer containing 1 mM MnCl_2 (final assay concentration ~ 100 pM); (iii) 2.5 μL of compound solution or DMSO; (iv) and 0.5×10^6 cells in a volume of 30 μL . The plates were incubated at room temperature for 30 minutes, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 μL of binding buffer containing 1 mM MnCl_2 . After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat# 6005178), 100 μL of Microscint-20 (Packard cat#

6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition. Control wells in which cells were omitted were used to determine the level of binding corresponding to 100% inhibition. Binding of ^{125}I -VCAM-Ig in the absence of cells was usually less than 5% of that observed using cells in the presence of vehicle. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

EXAMPLE 67

Antagonism of $\alpha_4\beta_7$ Dependent Binding to VCAM-Ig Fusion Protein.

15

Step A. $\alpha_4\beta_7$ Cell line.

RPML-8866 cells (a human B cell line $\alpha_4^+\beta_7^+$; a gift from Prof. John Wilkins, University of Manitoba, Canada) were grown in RPMI/10% fetal calf serum/ 100 U penicillin/100 μg streptomycin/2 mM L-glutamine at 37°C, 5 % carbon dioxide. The cells were pelleted at 1000 rpm for 5 minutes and then washed twice and resuspended in binding buffer (25 mM Hepes, 150 mM NaCl, 0.1 % BSA, 3 mM KCl, 2 mM Glucose, pH 7.4).

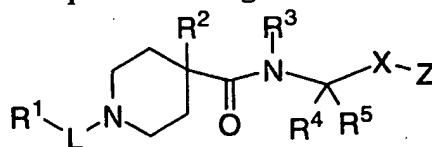
25 Step B. VCAM-Ig Binding Assay.

Compounds of this invention were prepared in DMSO at 100x the desired final assay concentration. Final concentrations were selected from a range between 0.001 nM-100 μM . Compounds were assayed in Millipore MHVB multiscreen plates (Cat# MHVBN4550) by making the following sequential additions to duplicate wells: (i) 100 μl /well of binding buffer containing 1.5 mM MnCl_2 ; (ii) 10 μl /well ^{125}I -VCAM-Ig in binding buffer (final assay concentration < 500 pM); (iii) 1.5 μl /well test compound or DMSO alone; (iv) 38 μl /well RPML-8866 cell suspension (1.25×10^6 cells/well). The plates were incubated at room

- temperature for 45 minutes on a plate shaker at 200 rpm, filtered on a vacuum box, and washed on the same apparatus by the addition of 100 μ L of binding buffer containing 1 mM MnCl_2 . After insertion of the multiscreen plates into adapter plates (Packard, Meriden, CT, cat#
- 5 6005178), 100 μ L of Microscint-20 (Packard cat# 6013621) was added to each well. The plates were then sealed, placed on a shaker for 30 seconds, and counted on a Topcount microplate scintillation counter (Packard). Control wells containing DMSO alone were used to determine the level of VCAM-Ig binding corresponding to 0% inhibition.
- 10 Wells in which cells were omitted were used to determine the level of binding corresponding to 100% inhibition. Percent inhibition was then calculated for each test well and the IC_{50} was determined from a ten point titration using a validated four parameter fit algorithm.

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

or a pharmaceutically acceptable salt thereof wherein:

- | | | |
|-------------------|----|-------------------------------------------|
| L is | 1) | -C(O)-, |
| | 2) | -O-C(O)-, |
| | 3) | -NR ^e -C(O)-, |
| | 4) | -S(O) ₂ -, |
| | 5) | -P(O)(OR ⁴)-, |
| | 6) | -C(O)C(O)-; |
| X is | 1) | a bond or |
| | 2) | C(R ⁶)(R ⁷); |
| Z is | 1) | -C(O)OR ^d , |
| | 2) | -P(O)(OR ^d)(OR ^e) |
| | 3) | -P(O)(R ^d)(OR ^e) |
| | 4) | -S(O) _m OR ^d , |
| | 5) | -C(O)NR ^d R ^h , or |
| | 6) | -5-tetrazolyl; |
| R ¹ is | 1) | C ₁ -10alkyl, |
| | 2) | C ₂ -10alkenyl, |
| | 3) | C ₂ -10alkynyl, |
| | 4) | Cy, |
| | 5) | Cy-C ₁ -10alkyl, |
| | 6) | Cy-C ₂ -10alkenyl, |
| | 7) | Cy-C ₂ -10alkynyl, |

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy is optionally substituted with one to four substituents independently selected from R^b;

R² is 1) a group selected from R¹;

R³ is

- 1) hydrogen,
- 2) C₁₋₁₀alkyl optionally substituted with one to four substituents independently selected from R^a, or
- 3) Cy optionally substituted with one to four substituents independently selected from R^b,

R⁴ is

- 1) hydrogen,
- 2) C₁₋₁₀alkyl,
- 3) C₂₋₁₀alkenyl,
- 4) C₂₋₁₀alkynyl,
- 5) Cy, or
- 6) Cy-C₁₋₁₀alkyl,

wherein alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b;

R⁵ is

- 1) hydrogen,
- 2) C₁₋₁₀alkyl,
- 3) C₂₋₁₀alkenyl,
- 4) C₂₋₁₀alkynyl,
- 5) Cy-(Cy¹)_p,
- 6) Cy-(Cy¹)_p-C₁₋₁₀alkyl,
- 7) Cy-(Cy¹)_p-C₂₋₁₀alkenyl,
- 8) Cy-(Cy¹)_p-C₂₋₁₀alkynyl,

alkyl, alkenyl and alkynyl are optionally substituted with one to four substituents independently selected from R^a; and Cy and Cy¹ are optionally substituted with one to four substituents independently selected from R^b;

R⁶ is

- 1) hydrogen,
- 2) a group selected from R^a, or
- 3) a group selected from R¹;

R⁷ is

- 1) hydrogen,
- 2) C₁₋₁₀alkyl,
- 3) C₂₋₁₀alkenyl,
- 4) C₂₋₁₀alkynyl,
- 5) Cy, or

6) Cy C1-10alkyl,

wherein alkyl, alkenyl, alkynyl are optionally substituted with one to four substituents selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b;

- R^a is
- 1) -CF₃;
 - 2) -OR^d,
 - 3) -NO₂,
 - 4) halogen
 - 5) -S(O)_mR^d,
 - 6) -CR^d(N-OR^e),
 - 7) -S(O)₂OR^d,
 - 8) -S(O)_mNR^dRe,
 - 9) -NR^dRe,
 - 10) -O(CR^fR^g)_nNR^dRe,
 - 11) -C(O)R^d,
 - 12) -CO₂R^d,
 - 13) -CO₂(CR^fR^g)_nCONR^dRe,
 - 14) -OC(O)R^d,
 - 15) -CN,
 - 16) -C(O)NR^dRe,
 - 17) -NR^dC(O)R^e,
 - 18) -OC(O)NR^dRe,
 - 19) -NR^dC(O)OR^e, or
 - 20) -NR^dC(O)NR^dRe;

- R^b is
- 1) a group selected from R^a,
 - 2) C1-10 alkyl,
 - 3) C2-10 alkenyl,
 - 4) C2-10 alkynyl,
 - 5) Cy, or
 - 6) Cy-C1-10 alkyl,

wherein alkyl, alkenyl, alkynyl, and Cy are optionally substituted with a group independently selected from R^c;

- R^c is
- 1) halogen,
 - 2) amino,

- 3) carboxy,
- 4) C₁₋₄alkyl,
- 5) C₁₋₄alkoxy,
- 6) hydroxy,
- 7) aryl,
- 8) aryl C₁₋₄alkyl, or
- 9) aryloxy;

R^d and R^e are independently selected from the group consisting of

- 1) hydrogen,
- 2) C₁₋₁₀alkyl,
- 3) C₂₋₁₀alkenyl,
- 4) C₂₋₁₀alkynyl,
- 5) Cy, and
- 6) Cy C₁₋₁₀alkyl,

wherein alkyl, alkenyl, alkynyl and Cy is optionally substituted with one to four substituents independently selected from R^c; or

R^d and R^e together with the atoms to which they are attached form a heterocyclic ring of 5 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and nitrogen; R^f and R^g are independently selected from hydrogen, C₁₋₁₀alkyl, Cy and Cy C₁₋₁₀alkyl; or

R^f and R^g together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

- R^h is
- 1) hydrogen,
 - 2) C₁₋₁₀alkyl,
 - 3) C₂₋₁₀alkenyl,
 - 4) C₂₋₁₀alkynyl,
 - 5) cyano,
 - 6) aryl,
 - 7) aryl C₁₋₁₀alkyl,
 - 8) heteroaryl,
 - 9) heteroaryl C₁₋₁₀alkyl, or
 - 10) -SO₂Rⁱ;

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a ; and aryl and heteroaryl are each optionally substituted with one to four substituents independently selected from R^b ;

R^i is

- 1) C₁₋₁₀alkyl,
- 2) C₂₋₁₀alkenyl,
- 3) C₂₋₁₀alkynyl, or
- 4) aryl;

wherein alkyl, alkenyl, alkynyl and aryl are each optionally substituted with one to four substituents independently selected from R^c ;

Cy and Cy¹ are independently selected

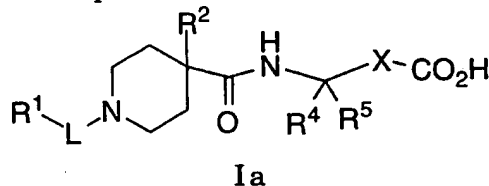
- 1) cycloalkyl,
- 2) heterocyclyl,
- 3) aryl, and
- 4) heteroaryl;

m is 0, 1 or 2;

n is an integer from 1 to 10; and

p is 0 or 1.

2. A compound of Claim 1 having the formula Ia:



wherein

L is

- 1) -C(O)- or
- 2) -S(O)₂;

X is

- 1) a bond or
- 2) C(R⁶)(R⁷);

R¹ is

- 1) C₁₋₁₀alkyl,
- 2) Cy, or
- 3) Cy-C₁₋₁₀alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a ; and Cy is optionally substituted with one to four substituents independently selected from R^b ;

R^2 is 1) a group selected from R^1 ;

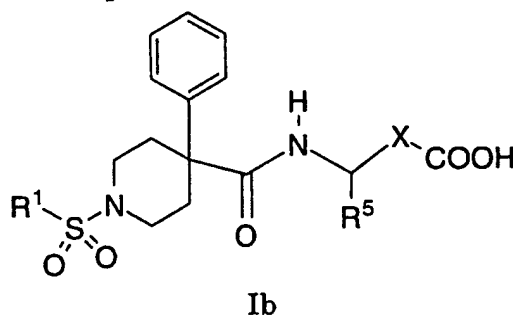
R^4 is 1) hydrogen;

R^6 is 1) hydrogen, or
2) a group selected from R^1 ;

R^7 is 1) hydrogen;

all the other variables are as defined in Claim 1.

3. A compound of Claim 1 having the formula Ib:



wherein

X is 1) a bond or
2) CH_2 ;

R^1 is 1) C_{1-10} alkyl,
2) Cy, or
3) Cy-C_{1-10} alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a ; and Cy is optionally substituted with one to two substituents independently selected from R^b ;

R^5 is 1) hydrogen,
2) C_{1-10} alkyl,
3) $\text{Cy-(Cy}^1)_p$, or
4) $\text{Cy-(Cy}^1)_p\text{-C}_{1-10}$ alkyl,

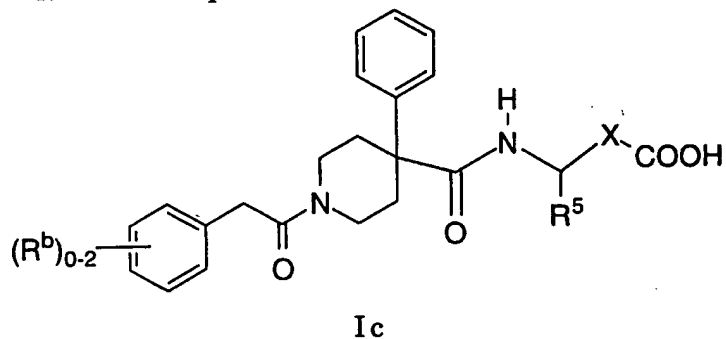
wherein alkyl is optionally substituted with one to two substituents independently selected from R^a ; and Cy and Cy^1 are optionally substituted with one to two substituents independently selected from R^b ;

Cy and Cy¹ are independently

1) aryl; and

all other variables are as defined in Claim 1.

4. A compound of Claim 1 having the formula Ic:



wherein

X is 1) a bond or

2) CH₂;

R⁵ is 1) hydrogen,

2) C₁-10alkyl,

3) (Cy)_p, or

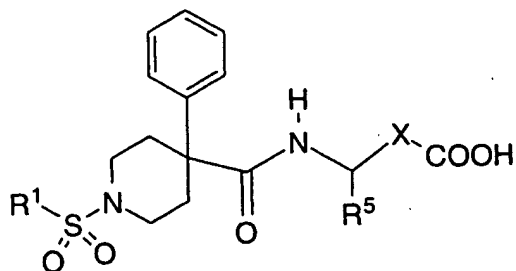
4) (Cy)_p-C₁-10alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy is optionally optionally substituted with one to two substituents independently selected from R^b;

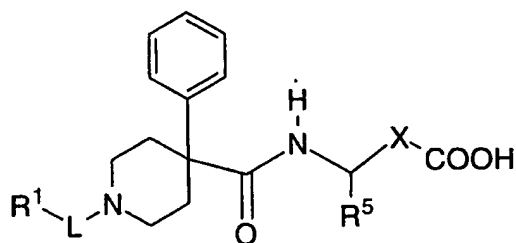
Cy is 1) aryl; and

all other variables are as defined in Claim 1.

5. A compound of Claim 1 selected from the group consisting of:

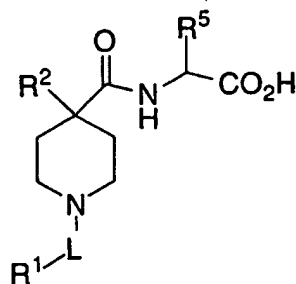


| <u>X</u> | <u>R1</u> | <u>R5</u> |
|----------|----------------|---------------------|
| - | 3,5-diCl-Ph | n-butyl |
| - | 3,5-diCl-Ph | benzyl |
| - | 3,5-diCl-Ph | phenyl* |
| - | 3,5-diCl-Ph | (4-biphenyl) methyl |
| CH2 | 3,5-diCl-Ph | methy*1 |
| CH2 | 3,5-diCl-Ph | benzyl* |
| CH2 | 3,5-diCl-Ph | isopropyl* |
| CH2 | 3,5-diCl-Ph | phenyl* |
| CHMe* | 3,5-diCl-Ph | H |
| - | n-C4H9 | benzyl |
| - | n-C8H17 | benzyl |
| - | Ph | benzyl |
| - | 4-F-Ph | benzyl |
| - | 3,5-diCl-Ph | benzyl |
| - | 4-CH3O-Ph | benzyl |
| - | 4-CH3C(O)NH-Ph | benzyl |
| - | 4-CF3O-Ph | benzyl |
| - | 3-CF3-Ph | benzyl |
| - | 3,5-di(CF3)Ph | benzyl |
| - | 3-CH3-Ph | benzyl |
| - | 3-CN-Ph | benzyl |
| - | 3-Cl-Ph | benzyl |
| - | 3-F-Ph | benzyl |



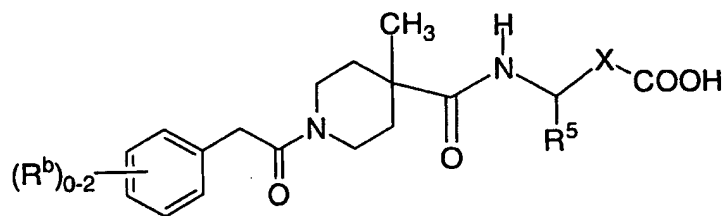
| <u>X</u> | <u>R1-L</u> | <u>R5</u> |
|----------|-------------|-----------|
| - | 2-MPUPA** | n-pentyl |

| | | |
|-----------------|------------------------------------------|---------------------|
| - | 2-MPUPA | benzyl |
| - | 2-MPUPA | phenyl* |
| - | 2-MPUPA | (4-biphenyl) methyl |
| CH ₂ | 2-MPUPA | methyl* |
| CH ₂ | 2-MPUPA | benzyl* |
| CH ₂ | 2-MPUPA | isobutyl* |
| CH ₂ | 2-MPUPA | phenyl* |
| CHMe* | 2-MPUPA | H |
| - | 2-MPUPA | 4-tBuO-benzyl |
| - | 2-MPUPA | methyl |
| - | 2-MPUPA | benzyl# |
| - | 2-MPUPA | 4-fluorobenzyl |
| - | 9-fluorenylmethoxy carbonyl | 4-fluorobenzyl |
| - | benzoyl | 4-fluorobenzyl |
| - | phenylacetyl | 4-fluorobenzyl |
| - | phenylcarbamoyl | 4-fluorobenzyl |
| - | 4-(benzamido) phenylacetyl | 4-fluorobenzyl |
| - | 4-(phenylacetamido) phenylacetyl | 4-fluorobenzyl |
| - | 4-(2-Me-phenylacet amido)phenylacetyl | 4-fluorobenzyl |
| - | PUPA | 4-fluorobenzyl |
| - | 2-MPUPA | 4-fluorobenzyl |
| - | 3-MPUPA | 4-fluorobenzyl |
| - | 4-MPUPA | 4-fluorobenzyl |
| - | 4-(PhOC(O)NH) phenylacetyl | 4-fluorobenzyl |
| - | 2-MPUPA | t-BuO-C(O)- methyl |
| - | 2-MPUPA | t-BuO-C(O)NH-butyl |
| - | 2-MPUPA | t-BuO-methyl |
| - | 2-MPUPA | carboxymethyl |



| <u>R²</u> | <u>R¹-L</u> | <u>R⁵</u> |
|---------------------------------|-----------------------------|------------------------------|
| CH ₃ | 2-MPUPA | (4-tBuO)benzyl |
| CH ₃ | 2-MPUPA | t-BuO-C(O)-methyl |
| CH ₃ | 2-MPUPA | n-butyl |
| CH ₃ | 2-MPUPA | benzyl |
| CH ₃ | 2-MPUPA | methyl |
| CH ₃ | 3,5-diCl-Ph-SO ₂ | (4-biphenyl) methyl |
| n-C ₄ H ₉ | 2-MPUPA | 4-fluorobenzyl |
| 4-F-Ph-CH ₂ | 2-MPUPA | 4-fluorobenzyl |
| CH ₃ | 2-MPUPA | 4-fluorobenzyl |
| CH ₃ | 2-MPUPA | 4-hydroxybenzyl |
| CH ₃ | 2-MPUPA | 4-carboxymethyl |
| CH ₃ | acetyl | 2'-methoxy-4-biphenylmethyl. |

6. A compound of Claim 1 having the formula Id:



Id

- X is
- 1) a bond or
 - 2) CH₂;
- R⁵ is
- 1) hydrogen,

- 2) C₁₋₁₀alkyl,
- 3) (Cy¹)_p, or
- 4) (Cy¹)_p-C₁₋₁₀alkyl,

wherein alkyl is optionally substituted with one to two substituents independently selected from R^a; and Cy and Cy¹ are optionally substituted with one to two substituents independently selected from R^b; Cy and Cy¹ are independently

- 1) aryl; and

all other variables are as defined in Claim 1.

7. A method for inhibiting cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

8. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

9. A method for the treatment of asthma in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

10. A method for the treatment of allergic rhinitis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

11. A method for the treatment of multiple sclerosis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

12. A method for the treatment of atherosclerosis in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

13. A method for the treatment of inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

14. A method for the treatment of inflammatory bowel disease in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 1.

15. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier thereof.

16. A method for inhibiting cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

17. A method for the treatment of diseases, disorders, conditions or symptoms mediated by cell adhesion in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

18. A method for the treatment of asthma, allergic rhinitis, multiple sclerosis, atherosclerosis or inflammation in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 2.

19. A pharmaceutical composition which comprises a compound of Claim 2 and a pharmaceutically acceptable carrier thereof.

INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US98/24513

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : 546/225, 226, 227, 228, 245; 514/313

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/225, 226, 227, 228, 245; 514/313

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | JP 08-277285 A (OOKUBO, M. et al) 22 October 1996, CA 126: 47110, RN 184715-74, RN 184715-75. | 1-19 |
| Y | WO 97/03094 A1 (BIOGEN, INC.) 30 January 1997, Table 1 pages 24-42, RN 187735-25-7p. | 1-19 |
| X | WO 95/08536 A1 (FUJISAWA PHARMACEUTICAL CO., LTD) 30 March 1995, Formula II, CA 123: 285788. | 1-19 |
| X | WO 89/10752 A1 (ABBOTT LABORATORIES) 16 November 1989, Chemical Abstract 114:247788 Vol. 114, 1991, RN 129739-41-9p. | 1-19 |
| A,P | US 5,770,575 A (BEAVERS et al.) 23 June 1998, Column 1 and 2. | 1,3,4,6-19 |

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents: | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| *A* document defining the general state of the art which is not considered to be of particular relevance | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| *E* earlier document published on or after the international filing date | *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | *G* document member of the same patent family |
| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

22 JANUARY 1999

Date of mailing of the international search report

18 FEB 1999

 Name and mailing address of the ISA/US
 Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

RITA DESAI

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/24513

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 211/30, 211/06, 211/60; A01N 43/40